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Ambient Water Quality Criteria: Acrylonitrile

(U.S.) Environmental Protection Agency, Washington, DC

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ACRYLONITRILE

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
Washington, D.C.

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Criteria and Standards Div.

Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for acrylonitrile. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itsel,...

KEYWORDS: *Water quality, *Toxicology, *Acrylonitriles, *Toxic substances, *Water pollution effects(Humans).

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March 23, 1979

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CRITERION DOCUMENTS

ACRYLONITRILE

CRITERIA

Aquatic Life

For acrylonitrile the criterion to protect freshwater aquatic life as derived using the Guidelines is 130 μg/l as a 24-hour average and the concentration should not exceed 300 μg/l at any time.

For acrylonitrile the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 130 μg/l as a 24-hour average and the concentration should not exceed 290 μg/l at any time.

Human Health

For the maximum protection of human health from the potential carcinogenic effects of exposure to acrylonitrile through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of acrylonitrile estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100,000 are presented in the Criterion Formulation section of this document. The Agency is considering setting criteria at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of 0.08 μg/l, 0.008 μg/l, and 0.0008 μg/l, respectively. If water alone is consumed, the water concentration should be less than 0.16 μg/l to keep the lifetime cancer risk below 10^{-5}.

ACRYLONITRILE

Introduction

Acrylonitrile is an explosive, flammable liquid having a normal boiling point of 77°C and a vapor pressure of 80 torr (20°C). The toxic effects of acrylonitrile are similar to cyanide poisoning although not identical. The chemical structure of acrylonitrile, $CH_2=CHCN$, resembles that of vinyl chloride, a material known to cause human cancer.

At present 1.6 billion pounds per year of acrylonitrile are manufactured in the United States. The major use of acrylonitrile is in the manufacture of copolymers for the production of acrylic and modacryclic fibers by copolymerization with methyl acrylate, methyl methacrylate, vinyl acetate, vinyl chloride, or vinlyidene chloride (Natl. Inst. Occup. Safety Health, 1977). Other major uses of acrylonitrile include the manufacture of acrylonitirile-butadiene-styrene (ABS) and styrene-acrylonitrile (SAN) resins (used to produce a variety of plastic products), nitrile elastomers and latexes, and other chemicals (e.g., adiponitrile, acrylamide). Acrylonitrile has been used as a fumigant; however, all U.S. registrations for this use were voluntarily withdrawn as of August 8, 1978 (43 FR 35099). The U.S. Food and Drug Administration has recently banned the use of an acrylonitrile resin for soft drink bottles (Chem. Eng. News, 1977, 1978), but its use is still allowed in other food packaging. The National Institute for Occupational Safety and Health estimates that 125,000 persons are potentially exposed to acrylonitrile in the workplace (Natl. Inst. Occup. Safety Health, 1977).

Acrylonitrile has been reported as acutely toxic to fish at concentrations as low as 10,100 µg/l and to the invertebrate, Daphnia magna, at 7,550 µg/l. Chronic toxic effects were not seen in D. magna at concentrations up to and including 3,600 µg/l. The bluegill, Lepomis macrochirus, concentrated acrylonitrile in its tissues by a factor of 48. The only available datum for a saltwater organism is a 96-hour LC50 of 24,500 µg/l for the pinfish, Lagodon rhomboides (U.S. EPA, 1978).

At present the body of evidence produced in both toxicity studies on laboratory animals and occupational epidemiologic studies on man suggests that acrylonitrile may be a human carcinogen. Thus, NIOSH has recently voiced its opinion that "acrylonitrile must be handled in the workplace as a suspect human carcinogen" (Natl. Inst. Occup. Safety Health, 1978). This judgment of NIOSH is based primarily on (1) a preliminary epidemiologic study of E.I. de Pont de Nemours and Co., Inc. on acrylonitrile polymerization workers from one particular textile fibers plant (Camden, S.C.); in this study, it was ascertained that a substantial excess risk (doubling over expected) of lung and colon cancers occurred between 1969 and 1975 in a cohort exposed between 1950 and 1955 (O'Berg, 1977); (2) interim results from ongoing 2-year studies on laboratory rats performed by Dow Chemical Co., and reported by the Manufacturing Chemists Association (April, 1977) (as cited in Federal Register) in which, by either drinking water or inhalation routes of acrylonitrile exposure, laboratory rats developed CNS tumors and zymbal gland carcinomas, not evident in control aminals. Mammary region masses were also in excess upon exposure to 80 ppm (Chem. Eng. News, 1978; Norris, 1977; Quast, et al. 1977).

Aside from suggestive evidence of carcinogenicity in man and animals, numerous workers have reported on the other genotoxic characteristics of acrylonitrile (embryotoxicity, mutagenicity, and teratogenicity) in laboratory animals (Venitt, et al. 1977; Milvey and Wolff, 1977; Murray, et al. 1976). Even though there is some controversy over the chronic effects of acrylonitrile (Shaffer, 1975), the acute toxicity of acrylonitrile is well known and the compound appears to exert part of its toxic effect through the release of inorganic cyanide (Fassett, 1963; Wilson, 1944).

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

No acute or chronic effects of acrylonitrile on freshwater aquatic life were observed at concentrations below approximately 2,600 µg/l. The 96-hour LC50 values for three fish species and the 48-hour EC50 for *Daphnia magna* range from 7,550 to 33,500 µg/l, which indicates that the probable range of sensitivity between fish and invertebrate species is not great.

Acute Toxicity

The sensitivity of fathead minnows to acrylonitrile has been tested under different test conditions and water quality (Henderson, et al. 1961). The pH values were 8.2 for hard water and 7.4 for soft water. These water quality characteristics apparently do not affect the toxicity of acrylonitrile. Flowthrough and static test conditions, using measured concentrations, were compared, and the unadjusted LC50 value was lower for the flowthrough test (10,100 µg/l) than for the static test (18,000 µg/l.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

The 96-hour unadjusted LC50 values were 14,300 and 18,100 µg/l at hardness concentrations of 380 and 29 mg/l as $CaCO_3$, respectively (Table 1). After adjustment for test conditions, the static LC50 is 12,851 µg/l. The adjusted 96-hour LC50 values for the bluegill, fathead minnow, and guppy (Henderson, et al. 1961) vary from 8,378 to 23,785 µg/l. The Final Fish Acute Value calculated from these data is 3,100 µg/l.

The only datum for freshwater invertebrate species is the 48-hour EC50 of 7,550 µg/l for *Daphnia magna* (Table 2). The Final Invertebrate Acute Value is 300 µg/l, and since this concentration is lower than the comparable value for fish, it also becomes the Final Acute Value for acrylonitrile.

Chronic Toxicity

Daphnia magna has been exposed for its life cycle and the results indicate no adverse effects at concentrations as high as 3,600 µg/l (Table 3). This concentration is only about 0.5 of the 48-hour EC50 (7,550 µg/l) for the same species under comparable conditions (U.S. EPA, 1978). This small difference between acute and chronic effects for *Daphnia magna* is unlike that relationship between acute and chronic effects for the fathead minnow. Henderson, et al. (1961), using flow-through methods and measured concentrations, observed a 96-hour LC50 of 10,100 µg/l (Table 1), and when that test was continued, the 30-day LC50 was 2,600 µg/l (Table 5).

The Final Invertebrate Chronic Value is greater than 710 µg/l, which is derived by dividing the chronic value for *Daphnia magna* by the sensitivity factor of 5.1 (Table 3).

Residues

The bluegill was exposed for 28 days to ^{14}C-acrylonitrile with thin layer chromatography being used to verify exposure and tissue concentrations (U.S. EPA, 1978). The bioconcentration factor for whole body was 48 with a half-life in the tissues of between four and seven days (Table 4).

Miscellaneous

As stated earlier, the 30-day LC50 for fathead minnows under flow-through conditions was 2,600 µg/l (Table 5), a result that is about one-fourth of the comparable 96-hour LC50 of 10,100 µg/l. Intermediate LC50 values were 6,900 µg/l after 10 days and 4,200 µg/l after 20 days. These data suggest that mortality would continue to occur even after 30 days. Henderson, et al. (1961) also exposed adult bluegill to 5,000 µg/l for 1 to 4 weeks and prepared the fish for a taste study panel (Table 5). No flavor impairment was detected at that concentration, which was almost one-half of the 96-hour LC50 value for the bluegill as determined by the same investigators. It is therefore unlikely that acrylonitrile will impair the flavor of freshwater fish.

CRITERION FORMULATION

Freshwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 2,500 µg/l

Final Invertebrate Acute Value = 300 µg/l

Final Acute Value = 300 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = greater than 710 µg/l

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = greater than 710 µg/l

0.44 x Final Acute Value = 130 µg/l

The maximum concentration of acrylonitrile is the Final Acute Value of 300 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For acrylonitrile the criterion to protect freshwater aquatic life as derived using the Guidelines is 130 µg/l as a 24-hour average and the concentration should not exceed 300 µg/l at any time.

Table 1. Freshwater fish acute values for acrylonitrile

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Fathead minnow, *Pimephales promelas*	S	U	96	14,300	7,818	Henderson, et al. 1961
Fathead minnow, *Pimephales promelas*	S	U	96	18,100	9,895	Henderson, et al. 1961
Fathead minnow, *Pimephales promelas*	FT	U	96	10,100	7,777	Henderson, et al. 1961
Guppy, *Lebistes reticulatus*	S	U	96	33,500	18,314	Henderson, et al. 1961
Bluegill, *Lepomis macrochirus*	S	U	96	11,800	6,451	Henderson, et al. 1961
Bluegill, *Lepomis macrochirus*	S	U	96	10,100	5,522	U.S. EPA, 1978

* S = static, FT = flow-through

** U = unmeasured, M = measured

Geometric mean of adjusted values = 9,735 µg/l $\frac{9,735}{3.9}$ = 2,500 µg/l

Table 2. Freshwater invertebrate acute values for acrylonitrile (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)
Cladoceran, *Daphnia magna*	S	U	48	7,550	6,395

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* S = static

** U = unmeasured

Geometric mean of adjusted values = 6,395 µg/l $\frac{6,395}{21}$ = 300 µg/l

Table 3. Freshwater invertebrate chronic values for acrylonitrile (U.S. EPA, 1978)

Organism	Test*	Limits (µg/l)	Chronic Value (µg/l)
Cladoceran, *Daphnia magna*	LC	>3,600	>3,600

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* LC = life cycle or partial life cycle

Geometric mean of chronic values = >3,600 µg/l $\quad \frac{>3,600}{5.1} = >710$ µg/l

Lowest chronic value = >3,600 µg/l

Table 4. Freshwater residues for acrylonitrile (U.S. EPA, 1978)

Organism	Bioconcentration Factor	Time (days)
Bluegill, *Lepomis macrochirus*	48	28

Table 5. Other freshwater data for acrylonitrile

Organism	Test Duration	Effect	Result (ug/l)	Reference
Fathead minnow, *Pimephales promelas*	30 days	LC50	2,600	Henderson, et al. 1961
Bluegill, *Lepomis macrochirus*	1-4 wks	No detectable flavor impairment of tissues	5,000	Henderson, et al. 1961
Bluegill (fingerlings), *Lepomis macrochirus*	96 hrs	100% survival	10,000	Buzzell, et al. 1968

SALTWATER ORGANISMS

Introduction

The only datum for the effect of acrylonitrile on saltwater organisms is a 96-hour LC50 for the pinfish.

Acute Toxicity

The 96-hour LC50 value for the pinfish after use of the Guidelines adjustment factors is 8,840 µg/l (Table 6). The Final Fish Acute Value calculated from this result is 2,400 µg/l. The comparable value for freshwater fish is 3,100 µg/l, and based on this minimum amount of data, the sensitivity of freshwater and saltwater fish species may be similar.

CRITERION FORMULATION

Saltwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 2,400 µg/l

Final Invertebrate Acute Value = not available

Final Acute Value = 2,400 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = not available

0.44 x Final Acute Value = 1,100 µg/l

No saltwater criterion can be derived for acrylonitrile using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available.

However, results obtained with acrylonitrile and freshwater organisms indicate how a criterion may be derived.

For acrylonitrile and freshwater organisms, 0.44 times the Final Acute Value is less than the Final Chronic Value that is derived from results of a life cycle test with *Daphnia magna*. Therefore, it seems reasonable to estimate a criterion for acrylonitrile and saltwater organisms using 0.44 times the Final Acute Value. Both a Final Fish Acute Value and a Final Invertebrate Acute Value are available for acrylonitrile and freshwater organisms, and the Final Acute Value is based on the invertebrate value since it is the lower of the two. For saltwater organisms, only a Final Fish Acute Value is available. For freshwater organisms, the Final Invertebrate Acute Value divided by the Final Fish Acute Value is 300 - 2,500 µg/l = 0.12. Multiplying this value times the saltwater Final Fish Acute Value for acrylonitrile results in an estimated saltwater Final Invertebrate Acute Value of 0.12 x 2,400 µg/l = 290 µg/l. Thus the estimated Final Acute Value for acrylonitrile is 290 µg/l. Multiplying the Final Acute Value of 290 µg/l by 0.44 gives 130 µg/l.

The maximum concentration of acrylonitrile is the Final Acute Value of 290 µg/l, and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on saltwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For acrylonitrile the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 130 µg/l as a 24-hour average and the concentration should not exceed 290 µg/l at any time.

Table 6. Marine fish acute values for acrylonitrile (Daugherty & Garrett, 1951)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Pinfish (juvenile), *Lagodon rhomboides*	S	U	24	24,500	8,840

* S = static

** U = unmeasured

Geometric mean of adjusted values = 8,840 µg/l $\frac{8,840}{3.7} = 2,400$ µg/l

ACRYLONITRILE

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ACRYLONITRILE

Mammalian Toxicology and Human Health Effects

EXPOSURE

Introduction

Acrylonitrile is an explosive, flammable liquid having a normal boiling point of 77°C and a vapor pressure of 80 torr (20°C). The toxic effects of acrylonitrile are similar to cyanide poisoning although not identical. The chemical structure of acrylonitrile, $CH_2=CHCN$, resembles that of vinyl chloride, a material known to cause human cancer. Synonyms for acrylonitrile include cyanoethylene, 2-propenenitrile, VCN, and vinyl cyanide. Polymerization grade acrylonitrile contains a number of impurities and additives, namely, dimethylformamide, hydrogen peroxide, hydroxyanisole, methyl acrylate, phenyl ether-biphenyl mixture, sodium metabisulfite, sulfur dioxide, sulfuric acid, and titanium dioxide. (O'Berg letter, 1977).

At the present time 1.6 billion pounds per year of acrylonitrile are manufactured in the United States by the reaction of propylene with ammonia and oxygen in the presence of a catalyst. (A number of other processes are used outside the United States.) Current domestic producers of acrylonitrile are American Cyanamid Company (New Orleans, Louisiana), E. I. de Pont de Nemours Company, Inc. (Beaumont, Texas and Memphis, Tennessee), Monsanto Company (Chocolate Bayou, Texas), and The Standard Oil Company (Lima, Ohio).

The major use of acrylonitrile is in the manufacture of copolymers for the production of acrylic and modacrylic fibers by copolymerization with methyl acrylate, methyl methacrylate, vinyl acetate, vinyl chloride, or vinylidene chloride. Acrylic fibers, marketed under tradenames including Acrilan, Creslan, Orlon, and Zefran, are used in the manufacture of apparel, carpeting, blankets, draperies and upholstery. Some applications of modacrylic fibers are synthetic furs and hair wigs; tradenames for modacrylic fibers include Acrylan, Elura, SEF, and Verel. Acrylic and/or modacrylic fibers are manufactured from acrylonitrile by American Cyanamid Company (Milton, Florida), Dow Badishe Company (Williamsburg, Virginia), E. I. de Pont de Nemours and Company, Inc. (Camden, South Carolina and Waynesboro, Virginia), Eastman Kodak Company (Kingsport, Tennessee), and Monsanto Company (Decatur, Alabama) (NIOSH, 1977).

Other major uses of acrylonitrile include the manufacture of acrylonitrile-butadiene-styrene (ABS) and styrene-acrylonitrile (SAN) resins (used to produce a variety of plastic products), nitrile elastomers and latexes, and other chemicals (e.g., adiponitrile, acrylamide). Acrylonitrile has been used as a fumigant; however, all U.S. registrations for this use were voluntarily withdrawn as of August 8, 1978 (Federal Register, Vol. 43, p.35099). The U.S. Food and Drug Administration has recently banned the use of an acrylonitrile resin for soft drink bottles (Chem. Eng. News, Sept. 12, 1977; Jan. 23, 1978), but its use is still allowed in other food packaging. NIOSH estimates that 125,000 persons are potentially exposed to acrylonitrile in the workplace. (NIOSH, 1977).

At the present time, the body of evidence produced in both toxicity studies on laboratory animals and occupational epidemiologic studies on man suggests that acrylonitrile may be a human carcinogen. Thus, NIOSH has recently voiced its opinion that "acrylonitrile must be handled in the workplace as a suspect human carcinogen." (NIOSH, 1978). This judgment of NIOSH is based primarily on (1) a preliminary epidemiologic study of E. I. de Pont de Nemours and Company, Inc. on acrylonitrile polymerization workers from one particular textile fibers plant (Camden, South Carolina); in this study, it was ascertained that a substantial excess risk (doubling over expected) of lung and colon cancers occurred between 1969 and 1975 in a cohort exposed between 1950 and 1955 (O'Berg, 1977); (2) interim results from ongoing 2-year studies on laboratory rats performed by Dow Chemical Company, and reported by the Manufacturing Chemists Association (April, 1977) in which, by either drinking water or inhalation routes of acrylonitrile exposure, laboratory rats developed CNS tumors and zymbal gland carcinomas, not evident in control animals. Mammary region masses were also in excess upon exposure to 80 ppm (Chem. Eng. News, Jan. 23, 1978. Norris, 1977; Quast, et al. 1977)

Aside from suggestive evidence of carcinogenicity in man and animals, numerous workers have reported on the other genotoxic characteristics of acrylonitrile (embryotoxicity, mutagenicity and teratogenicity) in laboratory animals (Venitt, et al. 1977; Milvey and Wolff, 1977; Murray, et al. 1976). Even though there is some controversy over the chronic effects of acrylonitrile (Shaffer, 1975), the acute toxicity of acrylonitrile is well known and the compound appears to exert part of its toxic effect through the release of inorganic cyanide (Fassett, 1963; Wilson, 1944).

In this compilation of the human health effects and hazard evaluation of acrylonitrile, several reviews were consulted (Grahl, 1970; Fassett, 1963; NIOSH, 1978). Much of the literature relating to occupational exposure and epidemiology is either Russion or East European in origin and, for the most part, only abstracts of these works were consulted.

With regard to the contamination of water supplies with acrylonitrile, most of the work available on this subject is in the foreign literature and deals primarily with either the use of polyacrylonitrile for filtration of industrial wastes or the biological treatment of waste effluents from acrylonitrile plants (Verkhovykh, et al. 1975; Skakihara, et al. 1976; Pradt and Meidl, 1976). Research regarding the monitoring of acrylonitrile in drinking water was not available for consideration. This is not unexpected because of the fact that only recently have the possible genotoxic effects of acrylonitrile come to light.

Acrylonitrile is the most extensively produced aliphatic nitrile and ranks 45th on the list of high volume chemicals produced in the United States (Chem. Eng. News, May 1, 1978). The 1976 production of acrylonitrile was 1.6 billion pounds (Chem. Eng. News, May 1, 1978) which is approximately 7 times the 1960 production volume.

Approximately 125,000 individuals in the United States are exposed to acrylonitrile monomer during its manufacture and polymerization or during its molding to acrylonitrile-based polymers including Dralong T, Barex 210, Lopac, butadiene-acrylonitrile and polyacrylonitrile (NIOSH, 1977). Disposal of acrylic polymers, including polyacrylonitrile, by burning results in the release of acrylonitrile monomer (Rumber, 1971). Residual amounts of acrylonitrile monomer are released from fabrics such as underwear made of polyacrylonitrile fiber (Rapoport, et al. 1974), and from furniture and other items made of polyacrylonitrile plastics Volskii, 1973). The public may also be exposed to acrylonitrile by ingestion of food products which have leached residual acrylonitrile monomer from polyacrylonitrile packaging materials, such as commercial plastic wraps for foods. (Chem Eng. News, Feb. 28, 1977). This problem of acrylonitrile monomer leaching has led the Food and Drug Administration to ban the use of polyacrylonitrile plastic for beverage containers (Chem. Eng. News, April 26, 1976 and Feb. 21, 1977). Cigarette smoke has been shown by gas chromatographic analysis to contain aliphatic nitriles including acrylonitrile, propionitrile and methacrylonitrile (Izard and Testa, 1968). The presence of aliphatic nitriles in cigarette smoke may explain why Mallette (1943) found higher values of thiocyanate (a known metabolic product of acrylonitrile) in the blood and urine of acrylonitrile works who were smokers compared to non-smokers.

In brief, in addition to occupational exposure of those involved in the manufacture and processing of aliphatic nitriles, the public is exposed to acrylonitrile from the breakdown of the acrylonitrile-based polymers to monomers when the polymers are burned for disposal, by release of residual monomer from acrylic fibers and plastics, by leaching of monomer from food packaging, and from cigarette smoke.

Some environmental monitoring for acrylonitrile has been reported by the Midwest Research Institute (1978). Limited analyses of air, water and soils at several sources and ambient locations throughout the United States resulted in the occasional finding of acrylonitrile. The values obtained are summarized in Table 1.

TABLE 1

Location (Source)	Maximum Acrylonitrile Concentrations*		
	Air (Mg/m^3)	Water** (Mg/l)	Soil** (Mg/kg)
Fortier, Louisiana (American Cyanamid)	13.6	0.1	0.5***
Linden, New Jersey (American Cyanamid)	15.9	0.8	50
Texas City, Texas (Monsanto)	8.9	0.4	none detected
Decatur, Alabama (Monsanto)	4.2	3,600	none detected
Camden, S. Carolina (DuPont)	1.1	20	none detected
Waynesboro, Virginia (Du Pont)	7.0	none detected	none detected
Washington, West Virginia (Borg-Warner)	325	1.5	none detected

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* Analysis were performed at various time intervals. Values given are maximum values. Some samples at the same location may be lower or non-detectable.

** Source of water or soil samples not indicated.

*** Only one sample was found where acrylonitrile was at the detection limit of 0.5 mg/kg. All others were below detection.

**** Too low for GC/MS confirmation.

Ingestion from Water

While no data on monitoring of water supplies for the presence of acrylonitrile were found in the literature, potential problems may exist. Because toxic manifestations in animals have been elicited by this route of administration, this source of exposure is potentially an important one.

There are limited data on the fate of acrylonitrile in the aqueous environment. It is known that acrylonitrile is hydrated readily at 100°C by 84.5 percent sulfuric acid to produce acrylamide sulfate (Kirk and Othmer, 1967, p. 340). Whether this reaction occurs in the natural environment is unknown.

Acrylonitrile is known to undergo photodegradation to saturated derivatives. When left standing, especially in the presence of light, a yellow color may develop, poss-

TABLE 2

Solubility of Acrylonitrile in Water as a Function of Temperature (From Kirk and Othmer, 1967, pp. 338-350)

Temperature, ^{0}C	Solubility of Acrylonitrile in Water (grams/deciliter)
0	7.2
20	7.35
40	7.9
60	9.1

ibly due to polymerization (Kirk and Othmer, 1967). Acrylonitrile is also subject to biodegradation (Kuchinskii, et al. 1977; Panova, et al. 1977; Anon, 1977; Schnee, et al. 1977; Kato and Yamamura, 1976; Mikami, et al. 1974). Measurement of biochemical oxygen demand has shown 25-70 percent degradation within 10 days (Hann and Jensen, 1970). Zabezhinskaya, et al. (1962) studied the persistence of acrylonitrile in the water column, noting that at an initial concentration of 10 mg/l, only 46 percent remained after 24 hours, 19 percent after 48 hours, and 5 percent after 96 hours. This would tend to minimize the entry of acrylonitrile by this route of exposure. It would be of great value to have detailed data on the persistence of acrylonitrile in various aqueous environments. A study by Midwest Research Institute (1977) investigated the stability of 10 ppm acrylonitrile in distilled water and Mississippi River water. Little decomposition occurred after 23 days in distilled water. In river water, however, total decomposition occurred by day 6. Adjusting to a pH of 4 had a stabilizing effect in that 67 percent of acrylonitrile was present at 23 days.

Adjusting to a pH of 10 delayed decomposition up to 6 days but total decomposition occurred by day 23.

Possible sources of acrylonitrile in the aqueous environment - either surface water, ground water or drinking water - are: (a) dumping of chemical wastes, (b) leaching of wastes from industrial landfills or holding lagoons, (c) leaching of monomers from polymeric acrylonitrile, (d) precipitation from atmospheric rain, and (e) loss during transfer and transport. (Hardy, et al. 1973). The first four sources listed are worthy of additional comment, and are discussed below.

a) Dumping of chemical wastes: Acrylonitrile monomer waste products are dumped by industrial companies directly into surface waters or sewage. Acrylonitrile has been used as a fumigant for stored food stuffs either alone or in a mixture with carbon tetrachloride, (Fishbein, 1976), methylbromide (Dumas and Bond, 1977) and other chemicals (Heuser and Scudamore, 1968). Though no longer in use, stored quantities of these fumigants may be being dumped by the former manufacturers or the users.

The questions of biotransformations of acrylonitrile in waste water, its effect on bacteria and particularly on biological sewage treatment processes such as the activated sludge treatment process are poorly understood. However, Chekhovskaya, et al. (1966) have observed the effect on saprophytic microorganisms and on ammonification and nitrification of acrylonitrile and related compounds found in the waste waters from acrylonitrile production. It was found that acrylonitrile was utilized by saprophytic microorganisms in concentrations of 150 mg/l (ppm). Acrylonitrile in a concentration of 50 mg/l inhibited nitrification. This suggests that acrylonitrile, entering an activated sludge process in concentrations of 50 ppm or greater, may inhibit certain bacterial processes such as nitrification. Cherry, et al. (1956) reported that microbial activity could substantially reduce acrylonitrile concentrations of 10, 25 and 50 ppm. They noted also that while the two lower concentrations supported a mixed population of microorganisms, the 50 ppm concentrations favored the growth of fungi. This observation supports the findings of Chekhovskaya, et al. (1966) on inhibition of nitrification at 50 ppm and above. Other workers have shown similar reductions of acrylonitrile content in wastewater by microorganisms (Mikami, et al. 1974; Kato and Yamamura, 1976).

b) Leaching of wastes from industrial landfills or holding lagoons: Industrial chemical or pesticide wastes, placed in holding tanks or lagoons, may spill over into surface waters as a result of excessive rainfall. These same wastes may be buried in industrial landfills. If the buried containers are damaged, rainfall may leach out the acrylonitrile and providing that the soil is permeable, permit its movement into proximal ground water.

c) Leaching of monomers from polymeric acrylonitrile: It is well known that residual amounts of monomers are commonly retained in polymers; for example, vinyl chloride is leached out of PVC pipes and into drinking water (Dressman and McFarren, 1978). Russian investigators have reported that acrylonitrile and other monomers in finished polymers were detected in the range of 30-3000 ppm (Klescheva, et al. 1970). Therefore, the acrylonitrile monomer can be leached from waste polymers buried in landfills in the manner described in (b) above. Acrylonitrile is also leached out of polyacrylonitrile plastic bottles by water (National Resources Defense Council, 1976).

d) Precipitation of acrylonitrile from atmospheric rain: Acrylonitrile has a very high volatility of 112 torr at 25°C (Kirk and Othmer, 1967). Therefore, it will volatilize substantially from various sources even at room temperature. (See Inhalation as Source of Exposure, below). Being present in the atmophere either as vapor per se or as adsorbed film on particulates, it is susceptible to precipitation by rain or snow from the atmosphere and could end up either in surface or ground waters.

e) Release of acrylonitrile from transfer and transport accidents: Acrylonitrile may be spilled during the process of transfer and/or transportation. This may result in air and/or water contamination.

Ingestion from Food

The likelihood of acrylonitrile residues existing on food is great (Casarett and Doull, 1975, p. 444; Fishbein, 1976; Dumas and Bond, 1977; Heuser and Scudamore, 1968). Dumas and Bond (1977) noted that acrylonitrile was desorbed very slowly from foods depending on the type of commodity and aeration conditions. Polyacrylonitrile containers (margarine containers, wrapping material, etc.) retain residual amounts of the monomer which may then be leached into the food and subsequently ingested by the consumer (Federal Register, 1976 and National Resources Defense Council, 1976).

Although FDA has banned the use of polyacrylonitrile plastic in soft drink bottles (Chemical and Engineering News, 1977), attempts to lift this ban by the producing companies are in progress. The FDA has restricted the monomer residue to about 80 ppm in the finished products and a restriction to 11 ppm was pending as of 1976. (Federal Register, 1974, 1975, 1976; The National Resources Defense Council, 1976). The currently produced soft drink container includes about 20 ppm acrylonitrile of which as much as 0.3 ppm acrylonitrile and 0.2 ppm HCN are reported to leach into hot water. (National Resources Defense Council, 1976).

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the nineteen major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

A measured steady-state bioconcentration factor of 48 was obtained for acrylonitrile using bluegills containing about one percent lipids (U.S. EPA, 1978). An adjustment factor of 2.3/1.0 = 2.3 can be used to adjust the measured BCF from the 1.0 percent lipids of the bluegill to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for acrylonitrile and the edible portion of all aquatic organisms consumed by Americans is calculated to be 48 x 2.3 = 110.

Inhalation

The current estimate in the U.S. for the number of individuals involved in the manufacture and polymerization of acrylonitrile is 125,000 (NIOSH, 1978). Therefore, a considerable population is at high risk to occupational exposures, particularly through inhalation. Analyses of atmospheric air from an acrylic fiber plant in which a large fraction of the coworkers complained of symptoms of illness, revealed concentrations of acrylonitrile of 3-20 mg/m^3 (Orusev, et al. 1973).

Workers involved in acrylonitrile synthesis or its polymerization are not the only occupational groups subject to acrylonitrile exposure; workers in plastic (polyacrylonitrile) molding factories are similarly at risk (Scupakas, 1968). Scupakas (1968) studied the working conditions in an old factory producing thermosetting plastics by molding, and noted various toxic manifestations in employees including dermatitis, disorders of CNS, chronic upper respiratory tract irritation, and other symptomatology when the acrylonitrile concentration in the in-plant environment was 1.4 mg/m^3. However, various other compounds were present in the in-plant atmosphere including phenol, formaldehyde, ammonia, HCl, butyl phthalate and carbon monoxide. Timofievskaya (1968), and Duvall and Rubey (1973) reported that various types of acrylonitrile polymers underwent decomposition to various nitriles, NO_x, unsaturated hydrocarbons, etc. either under molding conditions (40-400°C) or heating (40-80°C) and/or burning (200-600°C). The nature of the products formed were highly dependent on combustion conditions and contained significant amounts of highly toxic compounds. Some of the polymers studied included Dramalon T; polyacrylonitrile fiber; Barex 210 (3:1 acrylonitrile-methylacrylate copolymer); Lopac (9:1 methacrylonitrile-styrene copolymer); and 1,3 butadiene-nitrile rubber. It is clear that burning of acrylic polymers, including polyacrylonitrile, represents a great potential occupational and/or environmental hazard due to the release of high concentrations of acrylonitrile, other substituted vinyl compounds, HCN, NO_x, and other undetermined compounds (Table 3).

TABLE 3

Pyrolysis of Lopac as a Function of Temperature
Using Porapak N Column
(Monsanto, 1973)

Pyrolysis Temperature(^{0}C)	Pyrolysis Products
116	no compound observed
188	NH_3 (trace)
230	NH_3
260	NH_3
260	NH_3
290	NH_3
330	NH_3; HCN (trace); acrylonitrile
500	Air; CO; CO_2; C_2H_2; NH_3, HCN; acetonitrile, acrylonitrile, propionitrile; pyrrole
570	Air; CO; CO_2; C_2H_4; C_2H_2; NH_3; HCN; acetonitrile; acrylonitrile; pyrrole
740	Air; CO; CO_2; C_2H_4; C_2H_2; NH_3; HCN; acetonitrile; acrylonitrile; pyrrole

In addition, it is likely that various significant interactions between the compounds occur (Hilado, et al. 1976; Le Moan and Chaigneau, 1977).

Though data are unavailable on monitoring the ambient atmosphere for the presence of acrylonitrile; the stack gases from synthesis and polymerization plants for acrylonitrile may well be discharging significant amounts into the atmosphere. As noted above, another potentially significant ambient source of acrylonitrile and related compounds in air is the outside burning of acrylonitrile polymers. While it is known that acrylonitrile reacts photochemically in the vapor phase (Kirk and Othmer, 1967), no detailed data were available to the authors on the actual reactivity ($t_{1/2}$) of acrylonitrile in the atmosphere in ppm or ppb concentrations.

Vol'skii, et al. (1973) have noted that the amount of plastic and synthetic rubber furniture on boats must be limited to 10.8 kg of LKF-2 plastic/m^3 air to avoid an accumulation of monomers such as acrylonitrile vaporizing under the influence of the unusual combination of living conditions (humidity, heat, and light). The authors recommend adequate ventilation. Undoubtedly, the same findings apply to homes. In a recent report, Rapoport, et al. (1974) have indicated that traces of acrylonitrile were detected in the air surrounding underwear made from polyacrylonitrile fibers. Acrylonitrile, and a variety of other nitriles, have been found by gas chromatography to be components of cigarette smoke; the amounts were not quantified. (Izard and Testa, 1968).

Inhalation has been reported to be the major route of exposure in lethal cases of acrylonitrile poisoning (Radimer, et al. 1974). When man breathes air containing 20 ug acrylonitrile/liter (20,000 $\mu g/m^3$) the average retention of acrylonitrile vapors was found to be 46 percent (Rogaczewska and Piotrowsky, 1968). A later study by Young, et al. (1977) found with rats that retention was greater than 90 percent (see Pharmacokinetics).

Dermal

Acrylonitrile has exhibited toxic effects on experimental animals by skin absorption (Hashimoto and Kanai, 1965; Egorov, et al. 1976). Anton'ev, et al. (1970) have reported that skin contact is one of the most important routes for acrylonitrile absorption in plant workers and that the absorption of acrylonitrile applied to the forearm

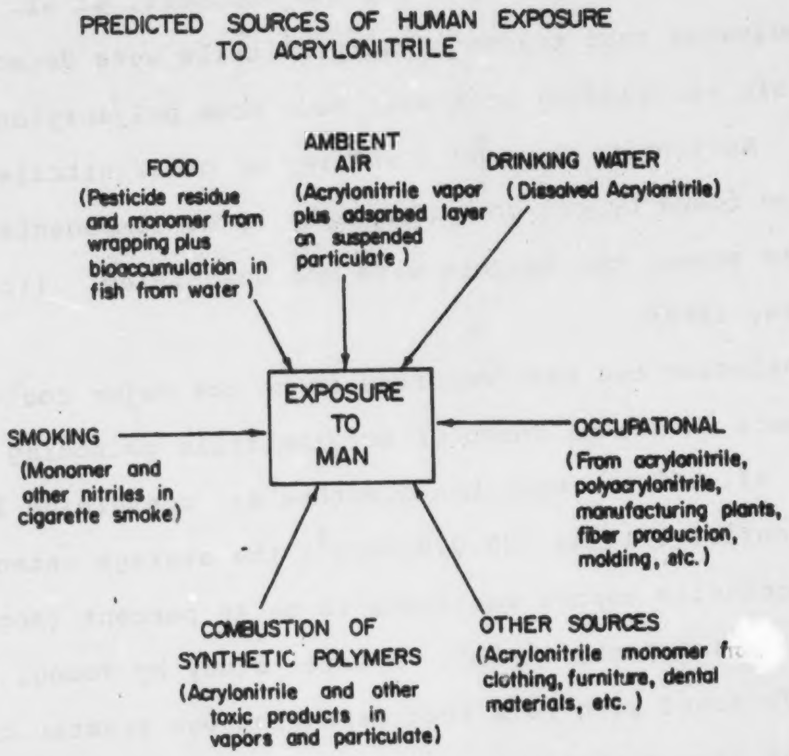

PREDICTED SOURCES OF HUMAN EXPOSURE TO ACRYLONITRILE
FOOD
(Pesticide residue and monomer from wrapping plus bioaccumulation in fish from water)
AMBIENT AIR
(Acrylonitrile vapor plus adsorbed layer on suspended particulate)
DRINKING WATER
(Dissolved Acrylonitrile)
SMOKING
(Monomer and other nitriles in cigarette smoke)
EXPOSURE TO MAN
OCCUPATIONAL
(From acrylonitrile, polyacrylonitrile, manufacturing plants, fiber production, molding, etc.)
COMBUSTION OF SYNTHETIC POLYMERS
(Acrylonitrile and other toxic products in vapors and particulate)
OTHER SOURCES
(Acrylonitrile monomer from clothing, furniture, dental materials, etc.)

Figure 1. Predicted Sources of Human Exposure.

skin averaged 0.6 mg/cm^2-hr. Egorov, et al. (1976) have determined the threshold doses for dermal absorption of acrylonitrile and other compounds in terms of a one-time application to the skin as well as a four-month long chronic application. The value for acrylonitrile was estimated to be 0.11 mg/kg body weight. The maximum permissible contamination level for the skin of the hands of workers was determined to be 0.7 mg of acrylonitrile. It is not clear from the abstract whether the experiment was done on laboratory animals and extrapolated to man or performed directly on man. Dermatologic conditions including contact allergic dermatitis, occupational eczema, and toxodermia in acrylonitrile workers have been discussed by Dovzhanskii, (1976), Balda (1975), Malten (1973), and Anton'ev, et al. (1970) and show the importance of the dermal route in occupational exposure. That there is a hypersensitivity response to acrylonitrile has been discussed by Dovzhanskii, (1976), Balda (1975) and Khromov (1974).

Because of the paucity of data available on acrylonitrile, it is difficult to assess quantitatively the contribution of each route of exposure to the total dose in man; it is likely that the greatest contribution comes _via_ inhalation, particularly in an occupational setting. The next most likely route is dermal and the least likely is ingestion. Figure 1 is a schematic representation of the various modes of exposure of man to acrylonitrile.

PHARMACOKINETICS

Absorption and Distribution

Attempts were not made to separate these categories due to the limited data available at the time of document preparation. Subsequently, a study on the pharmacokinetics of 1-^{14}C labelled acrylonitrile became available from the Manufacturing Chemists Association. Details of this study are included at the end of this chapter.

Blood concentrations of acrylonitrile and cyanide as a function of time after exposure have been studied in relation to toxicity (Hashimoto and Kanai, 1965). In the rabbit at a sublethal dose (30 mg/kg, LD50=75 mg/kg) a typical blood concentration versus time curve was observed. Acrylonitrile rapidly disappeared with 1 ppm of acrylonitrile remaining 4 hours after exposure. Thiosulfate accelerated the urinary excretion of SCN^- as a metabolite and somewhat reduced the toxicity of acrylonitrile; however, the blood concentration versus time curve was not changed (Hashimoto and Kanai, 1965). L-cysteine administered prior to acrylonitrile resulted in 80 percent reduction of acrylonitrile peak blood levels and 30 percent reduction of its toxicity. Unchanged acrylonitrile was detected in the urine of the rabbit 72 hours after exposure and in expired air 1 hour after dosing. In guinea pig urine, acrylonitrile was detected 24 hours after administration by gavage to 15 mg/kg (Hashimoto and Kanai, 1965). Urinary and expiratory excretion of unchanged acrylonitrile accounted respectively for only 3 and 10 percent of the dose (15 mg/kg) while urinary thiocyanate accounted for 14 percent of the dose (Hashimoto and Kanai, 1965). The remainder was probably metabolized via direct enzymatic or non-enzymatic conjugation with nucleophilic compounds such as, cysteine, glutathione, free or conjugated basic amino acids. Alternatively, the remainder may undergo enzymatic oxidation or reduction. A detailed metabolic study is required to elucidate the toxicokinetics of acrylonitrile.

Fat tissue accumulation of acrylonitrile may also occur. While the high solubility of acrylonitrile in water (7.35 percent at 20°C, Kirk and Othmer, 1967) would permit the excretion of the unchanged compound in the urine, the urinary detection 72 hours after exposure in the rabbit strongly suggests either fat storage or reversible protein binding. Czajkowska (1971) has studied the excretion of metabolites after a single i.p. dose (60-70 mg/kg) of acrylonitrile in rats. The main urinary metabolite in rats was SCN^-; its excretion within 72 hours amounted to 8.5 percent of acrylonitrile intake. The SCN^- excretion half-life was 13 hours. No cyanide was detected in rat urine within 24 hours following the single dose, while only traces of acrylonitrile were observed.

Metabolism

Earlier reports (Giacosa, 1883; Meurise, 1900) indicated that most aliphatic nitriles are metabolized to cyanide which is then detoxified to thiocyanate. Levels of cyanide and thiocyanate were elevated in the blood and present in the urine of acrylonitrile-treated animals. Brieger, et al. (1952) observed elevated levels of cyanide, thiocyanate (SCN^-) and cyanomethemoglobin in the blood of animals treated with acrylonitrile. It was concluded that acrylonitrile exerts its toxicity by the metabolic release of cyanide ion, and that the relative ability of various species to convert CN^- to SCN^- determined their susceptibility to the toxic action of acrylonitrile (Brieger, et al. 1952). It was found that the urinary excretion of thiocyanate after acrylonitrile administration ranged from 4-25 percent of the administered dose (Brieger, et al. 1952; Czajkowska, 1971; Gut, et al. 1975; Efremov, 1976; Paulet and Desnos, 1961; Benes and Cerna, 1959; Dudley and Neal, 1942; Hashimoto and Kanai, 1965). Brieger, et al. (1952) noted that in dogs (a species particularly susceptible to acrylonitrile), the relative concentration of cyanomethemoglobin increased with length of exposure, with most of the available methemoglobin converted to cyanomethemoglobin by the end of the lethal exposure period.

Using Wistar rats, albino mice and Chinese hamsters, Gut, et al. (1975) found that the extent of conversion of acrylonitrile to cyanide was dependent on the route of administration, decreasing in the following order: oral (20%) i.p. = S.C.(2-4%) i.v. (1%) (See Table 4). Thus, the more slowly acrylonitrile enters the system, the more extensively it is converted to cyanide. This suggests that conversion of acrylonitrile to cyanide involves metabolic processes competing with blood protein binding and non-enzymatic cyanoethylation. Pretreatment of rats with phenobarbital, SKF 525A, cysteine, or dimercaprol (BAL) did not significantly influence elimination of SCN^- in the urine after acrylonitrile administration; however, simultaneous administration of thiosulfate and acrylonitrile significantly increased the metabolized portion (thiocyanate) of acrylonitrile given to rats by two-fold and mice by 3-fold. Pretreatment with Aroclor 1254 was found to greatly enhance the toxicity of acrylonitrile, and to cause a 3-fold increase in the cyanide level in the blood of treated rats; Gut, et al. (1975) found acrylonitrile to be strongly bound in blood. Acrylonitrile was metabolized to SCN^- more effectively by mice than by rats following oral, i.p., and i.v. administration. Possible differences in the mechanism of acrylonitrile toxicity in rats and mice are indicated by the greater metabolism of acrylonitrile to SCN^- and the larger decrease in its acute toxicity by thiosulfate in mice compared with rats. Gut, et al. (1975) concluded that cyanide may play a more important role in the toxicity of acrylonitrile in mice than it does in rats.

TABLE 4

Influence of the Route of Administration of Acrylonitrile, 40 mg/kg (0.75 mM/kg) on Thiocyanate Elimination in Urine of Female Wistar Rats in Percent of Dose. (Data of Gut, et al. 1975)

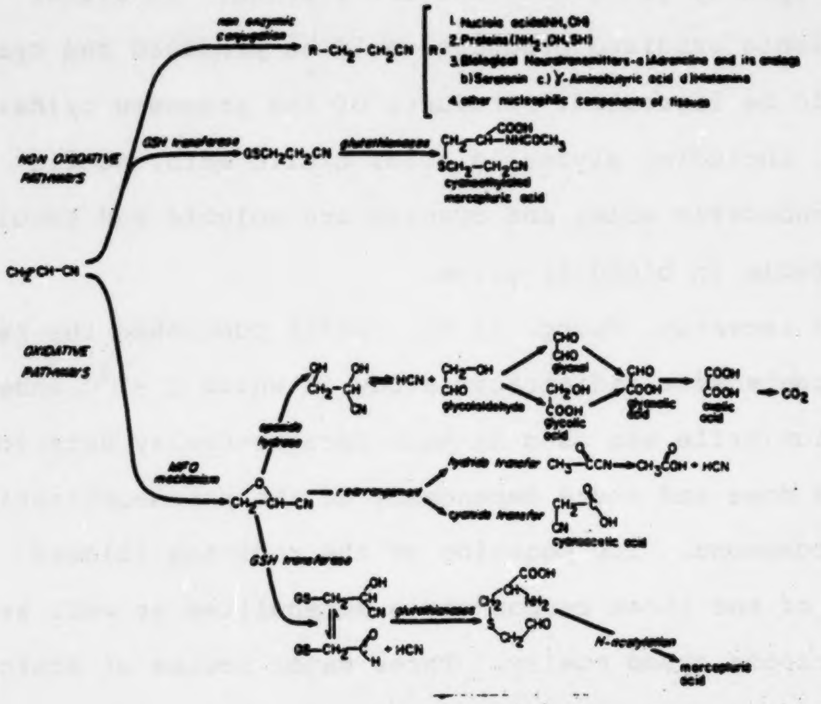
Expt. No.	Oral	i.p.	s.c.	i.v.
I	14.6 ± 3.0*	5.2 ± 0.4	4.6 ± 0.2	1.2 ± 0.5**
II	23.0 ± 3.2*	5.7 ± 0.4		
III	33.4 ± 4.0*	2.2 ± 0.1		
IV	21.4 ± 1.6*	2.9 ± 0.5		

All results represent Mean ± S.E.M., N = 5 to 6. Significantly different by Student's t test, p 0.05 from: *i.p., s.c. and i.v. administration; ** i.p. and s.c. administration.

In their study, Gut, et al. (1975) offered no explanation for the role of cysteine on the acrylonitrile SCN^- balance, nor do they explain cysteine's protective mechanism against acrylonitrile toxicity. If cysteine is protecting the animal by reaction with acrylonitrile via formation of cyanoethylcysteine, thiocyanate levels should decrease, and if it enhances cyanide metabolism, thiocyanate levels should increase. However, pretreatment with cysteine had no effect on thiocyante levels.

In vitro, it was implicated that acrylonitrile was conjugated with glutathione (GSH) via a GSH transferase enzyme. (The conjugate of this reaction was not detected; rather conjugation was measured indirectly by disappearance of the GSH substrate) (Boyland and Chasseaud, 1967). Although uptake of acrylonitrile gives rise to a slight increase in cyanomethemoglobin, combined therapy with nitrite and thiosulfate affords partial protection against its toxic action. These facts suggest that acrylonitrile toxicity is due in part to the acrylonitrile molecule itself or other unknown metabolite(s) rather than just the cyanide functional group. Only traces of unchanged acrylonitrile were detected in the urine of acrylonitrile-treated rats (Czajkowska, 1971). This suggests that the major portion of the compound is altered in the body to other metabolites or conjugates such as indicated in the following scheme proposed.

Proposed pathways for acrylonitrile biotransformation are presented in Figure 2. (A. Ahmed, personal communication). Cyanoethylated products (top pathway) of cell macromolecules and of circulating nucleophiles can be recovered



non enzymic conjugation
R–CH2–CH2CN
R=
1. Nucleic acids(NH,OH)
2. Proteins(NH2,OH,SH)
3. Biological Neurotransmitters-a)Adrenaline and its analogs
b)Serotonin c) γ-Aminobutyric acid d)Histamine
4. other nucleophilic components of tissues
GSH transferase
GSCH2CH2CN
glutathionases
COOH
CH2–CH–NHCOCH3
SCH2–CH2CN
cyanoethylated
mercapturic acid
NON OXIDATIVE PATHWAYS
CH2=CH–CN
OXIDATIVE PATHWAYS
OH
CH2–CH
OH
CN
HCN +
CH2–OH
CHO
glycolaldehyde
CHO
CHO
glyoxal
CH2OH
COOH
Glycolic acid
CHO
COOH
glyoxylic acid
COOH
COOH
oxalic acid
CO2
epoxide hydrase
MFO mechanism
O
CH2–CH–CN
rearrangement
hydride transfer
CH3–CCN
CH3COH + HCN
cyanide transfer
CH2–C
CN
OH
cyanoacetic acid
GSH transferase
GS–CH2–CH
OH
CN
glutathionases
COOH
CH
CH2
NH2
S
CH2
CHO
GS–CH2–C
O
H
+ HCN
N-acetylation
mercapturic acid

Figure 2. Proposed Pathways for Acrylonitrile Biotransformation.

in tissue fractions and in biologic fluids. If the proposed pathway is correct cyanoethylated glutathione conjugates should be recoverable in bile and urine. One, in fact, has been found - cyanoethylated mercapturic acid (Ahmed, personal communication). Oxidation by the mixed function oxidases or another enzyme system could lead to an epoxide which could be enzymically hydrated, could rearrange, or be acted upon by glutathathione transferase. In either case, soluble oxidized products would be produced and cyanide would be liberated. Products of the proposed oxidation pathways, including glyoxalic acid, oxalic acid, acetic acid, cyanoacetic acid, and cyanide are soluble and should be detectable in blood or urine.

Most recently, Young, et al. (1977) published the results of a comprehensive radiotracer study in which 1 -^{14}C labelled acrylonitrile was used in male Sprague-Dawley Rats to determine dose and route dependency of the pharmacokinetics of this compound. The position of the radiotag allowed tracking of the three carbon chain metabolites as well as the one carbon cyano moeity. Three major routes of administration were used with the following dose variations:

Route	Doses	
Ingestion via single oral dose of aqueous solution.	0.1 mg/kg	10 mg/kg
Inhalation of 6 hours duration from a "nose only" chamber	5 ppm Calc. mean dose = 0.7 mg/kg	100 ppm 10.2 mg/kg
Intravenous injection	10 mg/kg	

The major conclusions of this study are highlighted in the following:

Absorption: When orally administered to rats, essentially all of the acrylonitrile is absorbed and metabolized. Only 5 percent of the dose is excreted with the feces in the form of metabolites.

Metabolism: Qualitatively four metabolites, A, C, E and CO_2 were identified in the rat. Three of these (A,C,E) were excreted primarily in the urine, while CO_2, was primarily exhaled with breath. Chemical identities of compounds A, C, and E were not elucidated, but contrary to prior suspicion none of these were acrylamide. Metabolite C predominated at low doses followed by compound A while molecule E was present in trace quantities. This ratio changed at high dose when A drastically increased. Recovery of total radioactivity in metabolites, A, C, E and CO_2 exceeded 94 percent.

Distribution: The metabolites of acrylonitrile were rapidly distributed to all tissues. Plasma concentration of radioactivity remained at similar levels without regard to route or dose. Metabolites E and C were reabsorbed from the small intestine and metabolite E underwent enterohepatic circulation. The enterogastric and enterohepatic phenomena could account for the retention of the radioactivity in the body. Metabolite E was found in the erythrocytes, where its half-life was significantly longer than in other storage sites. This latter observation suggests that metabolite E forms adducts with red cell constituents. This in turn may imply that the red cell serves as an accumulator of chronic acrylonitrile insult in the body, and therefore may be used for biological monitoring of exposure. Independently of dose or route of administration metabolite E was selectively accumulated in the stomach (glandular and non-glandular portion of the stomach wall).

Even after the total body burden of ^{14}C declined and after the ^{14}C concentration of stomach contents diminished, the stomach uptake remained at a positive slope. This finding reinforces phenomena previously observed in rats, namely the emergence of gastric papillomas even though the route of exposure was other than oral.

In a similar fashion the skin accumulated acrylonitrile metabolites which rose to 2-3 fold over plasma levels. Possible interfering effects of skin absorption from the exogeneous gas phase must be discounted because the investigators used a "nose only" type of inhalation chamber. While the mechanism of skin absorption is unknown, it is plausible that the abundance of the sulfhydryl groups in the skin protein matrix may be responsible for the effects seen.

Dose dependency of metabolism: Metabolite C was found to be the main liver metabolite, which after bile excretion was readily re-absorbed from the small intestine and excreted in the urine. Only a very small portion of the total dose-load appeared in the form of compound A. After administration of high doses however, compound A strikingly increased. The formation of metabolite E was time dependent and did not occur significantly in the first eight hours after administration. An *in vitro* study using rat liver homogenate

(9000xg) supernate indicated that the liver is not the chief site for the formation of compound E. In addition, the very early appearance of metabolite E in the red cells suggests extrahepatic sites (perhaps a red cell enzyme) for the formation of this molecule.

The fourth metabolite, CO_2 could arise as a product of cyanate metabolism. Although thiocyanate was shown to be the main product of cyanide metabolism (Boxer and Richards, 1952) these authors have shown that cyanide can be metabolized to carbon dioxide via the cyanate ion. In fact, this study demonstrated a strong dose dependence of cyanide metabolism in dogs. It is plausible that the dose dependence of acrylonitrile pharmacokinecs may result in part from differences in the fate of the cyanide formed.

Excretion

The dose and route dependent variations in the metabolic fate of acrylonitrile are most likely due to shifts in metabolic pathways associated with hepatic and extrahepatic origin. Therefore the authors conclude: "extrapolation of the results of toxicological studies conducted by one route to expected toxicity at the same dosage by another route (a common practice) may not be valid for acrylonitrile because of its route dependent fate; likewise, extrapolation from toxicological data at one dose level to a different, untested, dose levels cannot be done with confidence because of the dose dependent fate of acrylonitrile in the body".

This conclusion creates some uncertainty in the use of the linear non-threshold model for calculating the acceptable risk concentration in water for man exposed to acrylonitrile (see section on Carcinogenicity, Criteria Formulation). However, the data presented by Young, et al. (1977) did not indicate that the metabolites whose fate was dose-dependent was necessarily the cancer inducing material. Therefore, until these data are experimentally developed the linear model can still be applied.

EFFECTS

Acute, Subacute and Chronic Toxicity

Dudley and Neal (1942) reported that a 4 hour exposure by inhalation to 635 ppm acrylonitrile was fatal to rats, while a 4 hour exposure to a lower level, 100 ppm, was fatal to dogs. Subsequent animal experiments have shown that acrylonitrile is acutely toxic by all routes of administration including inhalation, oral, subcutaneous and cutaneous exposure. (Toxic Substances List, 1977).

Table 5 lists the toxic effect levels for different species. (Toxic Substances List, 1977). Acrylonitrile toxicity varies between species (Wilson and McCormick, 1949). Mice are very sensitive to acrylonitrile and suffer a severe decrease in body weight with a slight change in blood picture (Hashimoto, 1962). Benes and Cerna (1959) observed that rats have higher resistance to acrylonitrile exposure; they developed delayed symptoms and high levels of thiocyanate in urine and blood. Dudley, et al. (1942) reported that inhalation exposure of rats to 56 ppm x 4 hours, 5 days a week, for 8 weeks resulted in irritation of the respiratory mucous membrane with hyperemia, lung edema, alveolar thickening and hemosiderosis of the spleen. Central nervous system disorders were also observed.

TABLE 5

Toxic Levels of Acrylonitrile for Different Species
(From Toxic Substances List, 1977)

Species	Route	Effect	Dose
Man	Inhalation	TCLo	16 ppm/20 min
Rat	Oral	LD50	82 mg/kg
	Inhalation	LCLo	500 ppm/4 hr
	S.C.	LD50	96 mg/kg
Mouse	Oral	LD50	27 mg/kg
	Inhalation	LCLo	784 ppm/hr
	I.P.	LCLo	15 mg/kg
Dog	Inhalation	LCLo	120 mg/kg/4hr
Cat	Inhalation	LCLo	600 ppm/4hr
Rabbit	Oral	LD50	43 mg/kg
	Inhalation	LCLo	258 ppm/4hr
	Skin	LD50	280 mg/kg
Guinea Pig	Oral	LD50	50 mg/kg
	Inhalation	LC50	576 ppm/4hr
	Skin	LD50	250 mg/kg

A 90-day toxicity study, conducted by Dow Chemical Company incorporating 200 and 300 ppm of acrylonitrile in the drinking water of rats resulted in the animals' death before the end of the study (National Resources Defense Council, 1976). Knobloch, et al. (1972) observed a perceptible change in peripheral blood pattern, functional disorders in the respiratory and cardiovascular systems and the execretory nephron system as well as signs of neuronal lesion in the CNS of rats and rabbits breathing acrylonitrile (50 mg/m^3 air) for 6 months. In addition, they reported irritation of the mucosa when acrylonitrile concentration in the air was increased to 250 mg/m^3. Graczyk, et al. (1973) reported that i.v. administration of 13-110 mg acrylonitrile decreased the pressor effects of epinephrine, norepinephrine and acetylcholine. When injected s.c. at 0.5 mg/rat/day for 10 days, acrylonitrile decreased the rate of O_2 uptake and increased that of glycolysis in brain (Solov'ev, et al. 1972). Acrylonitrile did not effect the levels of ATP or creatinine phosphate. Solov'ev, et al. also reported an increase in the activity of phosphofructokinase and a decrease in the glycogen level in cerebral tissue.

Knobloch, et al. (1971) reported that the LD50's of acrylonitrile in rats were 80 and 100 mg/kg when given s.c. and i.p., respectively, and 34 mg/kg when given s.c. to mice. When inhaled with air over three weeks, the LC50's of acrylonitrile were 0.3, 0.47 and 0.99 mg/l in mice, rats and guinea pigs, respectively (Knobloch, et al. 1971). They also reported that acrylonitrile caused congestion and damage to the CNS, lungs, liver and kidneys. I.p. injections of 50 mg acrylonitrile/kg daily for 3 weeks to adult rats resulted in body weight loss, leukocytosis, functional disturbances in liver and kidneys, slight damage to the neural cells of the brain stem and cortex and parenchymal degeneration of the liver and kidneys (Knoblock, et al. 1971). Krysiak and Knobloch (1971) reported that acrylonitrile (20 mg/kg/day for 6 weeks or 40 mg/kg/day for 4 weeks) caused disturbances in the central nervous system of rats as evidenced by misperformance in the labyrinth test. In that test acrylonitrile caused marked impairment of food-conditioned reflexes and learning ability. Babanov, et al. (1972) reported that inhalation of acrylonitrile vapor (0.495 mg/m^3, 5 hours/day, 6 days/week) for 6 months resulted in CNS disorders and an abnormal blood picture (increased erythrocyte count and decreased leukocyte count) in rats. It also resulted in increased total protein catalase and peroxidase content, decreased ascorbic acid content of blood serum and increased number of free sulfhydryl groups in the liver and blood serum. Acrylonitrile given orally in a dose of 80 mg/kg increased the content of several amino acids in the brain (Movsumzade, 1970). In the same study Movsumzade reported that, in the liver, various pools of basic amino acids levels were decreased to traces. He related these observations to the damage of synthetic function of the liver and to damage of the blood-brain barrier. Takagi, et al. (1968) studied the effect of administration of vitamins B_1 or B_2 plus cysteine to rats exposed to acrylonitrile vapor over a long period. They observed that urinary excretion of thiocyanate decreased with this treatment. They reported that exposure to acrylonitrile caused enlargement of liver, kidney, heart and spleen and a decline of alcohol dehydrogenase activity in the liver; alleviation of these symptoms occurred upon administration of Vitamin B_1 or B_2 plus cysteine. A single s.c. administration to rats of acrylonitrile at two times the LD50 dose decreased the liver and kidney glutathione level greatly and increased levels of lactic acid (Dinu and Rodica, 1976). These authors also reported that catalase activity was slightly increased but only in the liver. They concluded that the decrease of glutathione levels rendered the glutathione peroxidase ineffective, and the increase of lactic acid concentration concomitantly inhibited a compensatory increase in catalase activity. The resulting increase in peroxide level damaged the tissue. Dinu (1975) reported that similar doses of acrylonitrile administered orally to rats increased the hepatic levels of malonaldehyde, glutathione peroxidase and catalase, which she concluded, indicate lipid peroxidation.

Tissue protein and non-protein sulfhydryl decreased in guinea pigs and rabbits following a single dose of acrylonitrile (Hashimoto and Kanai, 1965; Szabo, et al. 1977; and Dinu, 1975). Prior treatment with thiol compounds such as cysteine, confers some protection against the toxic action of acrylonitrile (Paulet, et al. 1966; Hashimoto and Kanai, 1965). An increase in the number of free sulfhydryl groups was also observed in the liver and serum of rats chronically treated with acrylonitrile (Babanov, et al. 1972). In vitro inhibition of potassium-stimulated respiration of brain cortex was observed at a 10^{-3}M acrylonitrile concentration; little effect on liver respiration was observed. (Hashimoto and Kanai, 1965). Tarkowski (1968) reported that cytochrome oxidase was inhibited in liver, kidney, and brain tissue taken from rats 2 hours after i.p. administrations of 100 mg/kg acrylonitrile. In Tarkowski's in vitro experiments with similar tissues, inhibitions of 18-30 percent, 45-55 percent and 75-85 percent with 10^{-4}, 10^{-3} and 10^{-2}M acrylonitrile, respectively, were obtained. Since acrylonitrile did not change the spectrum of cytochrome oxidase in the same manner as KCN, Tarkowski concluded that the toxic effect of acrylonitrile could not be attributed to generation of cyanide. Minami, et al. (1973) reached just the opposite conclusion. They reported what they thought to be a high degree of similarity between the response of rabbits poisoned by acrylonitrile and rabbits poisoned by cyanide; the blood pO_2, pCO_2, pH, hemoglobin and hemotocrit values were correlated with the concentration of cyanide and thiocyanate.

Wilson and McCormick (1949) reported that acrylonitrile shows large variations in toxicity between species. In rabbits, extensive damage in the four phases of the brain nervous system was observed. Other symptoms were shivering, tearing, redness of the ears and hyperemia (Benes and Cerna, 1959). Dudley, et al. (1942) reported that guinea pigs treated with acrylonitrile (1.25 mg/l) developed strong interstitial nephritis, bronchopneumonia and inflammatory lung irritation. Dogs were the most sensitive experimental animals to acrylonitrile (Grahl, 1970). Thiocyanate levels in serum and urine of dogs treated with 100 ppm acrylonitrile were ten times higher than those of rats receiving the same dose (Lawton, et al. 1943 and Lindgren, et al. 1954). Liver and kidney damage was less pronounced in the dogs than in rats (Brieger, et al. 1952). In monkeys, anoxia, brain damage and death by suffocation were observed upon administration of acrylonitrile (Grahl, 1970). Acrylonitrile intoxication in cats resulted in the early onset of liver injury (Dudley, et al. 1942). Pathologic examination of animals following acute acrylonitrile exposure revealed all animals had edema (Dudley and Neal, 1942; Szabo and Selye, 1971); histologic changes in the brain, particularly the cortex, characteristic of anoxia (Brieger, et al. 1952); blood that was unusually dark red and liquid (Dudley and Neal, 1942; Brieger, et al. 1952); and liver and kidney damage (Knobloch, et al. 1972). Pathologic examination following repeated acrylonitrile administration revealed slight damage to the neural cells of the brain stem and cortex, and parenchymal cell degeneration of the liver (Knobloch, et al. 1971). Repeated acrylonitrile administration was also associated with weight loss, leukocytosis and functional disturbances of liver, kidney and adrenal cortex (Knobloch, et al. 1971; Szabo, et al. 1976). Szabo and Selye (1971) reported that adrenal apoplexy and necrosis were produced in rats by administration of a single oral dose of acrylonitrile (100-200 mg/kg), 100 percent mortality was observed. The adrenals of the dead animals showed hemorrhages in the cortex and necrosis in the inner cortical zones. Acrylonitrile induced-adrenal apoplexy, and mortality in female rats were both prevented by pretreatment with phenobarbital and adrencorticotrophic (ACTH) hormones (Szabo and Selye, 1971 and 1972). Szabo and Selye (1972) also reported that the adrenal lesion was abolished by the potent glucocorticoid, betamethason. Estradiol prevented adrenal apoplexy in approximately half the animals treated with a single lethal dose of acrylonitrile (Szabo and Selye, 1972). The mechanism by which these drugs interfered with the acrylonitrile induced injury is not clear (Szabo and Reynolds, 1975).

Few human studies, other than cancer epidemiology, were found for U.S. workers. Therefore, the majority of studies cited are from the foreign literature. Complete details of these studies were not available at the time of writing.

The human threshold of smell to acrylonitrile lies between 8-40 mg/m^3 (3.7-18.5 ppm), and a quick tolerance is always developed after repeated inhalation (Fairhall, 1957). A point of unbearability was reached at 800-1000 mg/m^3 (370-460 ppm) sometime after 70 seconds of exposure (Grahl, 1970). The high threshold of smell and the high absorptive capacity of environmental objects (such as textiles, wood, food and grain) to acrylonitrile acts to minimize the perception of acrylonitrile and so intensify the degree of exposure, and consequently the toxicity.

Goncharova, et al. (1977) reported that examinations of 689 persons engaged in the production of acrylonitrile in the USSR evidenced effects of acrylonitrile upon the heart. In their studies Shirshova, et al. (1975) indicated that workers with long service records in the acrylonitrile polymer industry showed decreases in hemoglobin level and a trend to leukopenia and relative lymphocytosis. Stamov, et al. (1976) studied the working environment and health state of workers involved in the production of polyacrylonitrile fibers (Burgas, Bulgaria) where dimethylformamide was also present. Their studies indicated that in exposed workers there is a tendency towards diseases of the peripheral nervous system, stomach, duodenum and skin.

In an epidemiologic study of health impairment among acrylonitrile workers in Japan, Sakarai and Kasumoto (1972) studied 576 workers exposed over a 10-year period (from 1960 to 1970) to acrylonitrile in concentrations of 5-20 ppm. The cohort was studied with respect to: a) age and length of exposure to acrylonitrile; b) subjective complaints as well as; c) objective symptoms. They found increased incidences of subjective complaints including headache, fatigue, nausea and weakness; as well as clinical symptoms of anemia, jaundice, conjunctivitis and abnormal values of specific gravity of whole blood, blood serum and cholinesterase values, urobilimogen, bilirubin, urinary protein and sugar. These clinical values were found to vary directly with length of exposure to acrylonitrile and differences were significantly different from normals. Sakarai and

Kasumoto (1972) concluded that acrylonitrile exposures at these levels caused mild liver injury and probably a cumulative general toxic effect.

The working conditions and health status of operators engaged in the production of acrylonitrile were studied by Ostrovskaya, et al. (1976), where the working area atmosphere was polluted by acrylonitrile as well as other chemicals. In those workers, changes in the heart and circulation, blood methemoglobin content, and increased excretion of glucuronic acid occurred during working hours.

Zotova (1975) in the U.S.S.R. reported that the concentration of acrylonitrile in the air of the plant he studied, exceeded by 5-10 fold the "maximal permissible concentration" (i.e., hygienic goal; 0.435 mg/m^3) and he recommended the enforcement of lower levels for the compound. He reported the blood of workers in contact with acrylonitrile, when compared with control values, had a lower content of erythrocytes, leukocytes, hemoglobin and sulfhydryl groups.

Shustov and Mavrina (1975) reported that medical examination of 340 workers and clinical studies of the blood and other biological fluids of 50 workers in polyacrylonitrile production plant showed symptoms of poisoning in the majority of the workers. They found that workers complain of headaches, vertigo, fatigue, insomnia, and skin itching. The clinical studies show that the majority of the workers have functional disorders of the central nervous system, cardiovascular and hemopoietic systems. The degree of pathological change increased with years of service in the plant (Shustov and Mavrina, 1975).

Dovzhanskii (1976a, 1976 b), Khromov (1974) and Balda (1975) reported contact allergic dermatitis and changes in immunoglobulin levels upon direct contact with acrylonitrile and other acrylate components of synthetic fabrics. Mavrina and Il'ina (1974) reported that students of an industrial training school, who came in contact with acrylates (mainly acrylonitrile), at atmospheric levels of 0.8-1.8 mg/m^3 showed disturbed immunological reactivity and sensitization. The positive allergic reactions in persons not having signs of allergic diseases indicated latent allergy (premorbid phase) developing at various times after contact with acrylonitrile. Because of the considerable sensitivity of young people, sensitization by these substances can develop within several days after the start of the training (Mavrina and Il'ina, 1974).

Recently Radimer, et al. (1974) reported four cases in which toxic epidermal necrosis developed 11-21 days after patients returned to houses fumigated with a 2:1 mixture of carbontetrachloride and acrylonitrile; this mixture was once widely used as a pesticide in Florida homes (Radimer, et al. 1974). In these cases, four patients were hospitalized with blisters covering almost the entire skin surface and mucous membranes. Administration of antibiotics, corticosteroids, fluids and electrolytes produced no improvement in the three adult female patients. These three patients died of septic shock and gastrointestinal hemorrhage 3-4 weeks after exposure (Radimer et al. 1974). They also reported that the ten-year-old son of one of these patients developed widespread pruritic eruptions, but survived with topical and parenteral corticosteroid application. The possibility that carbon tetrachloride rather than acrylonitrile, was the responsible agent for the observed toxicity cannot be excluded absolutely (Radimer, et al. 1974). Hardy, et al. (1972) reported an impaired pulmonary function following a railroad accident in which a crew of four railroad engineers suffered an intense single exposure to unknown amounts of acrylonitrile. After the exposure, weakness was the chief symptom followed by dyspnea on exertion when the workers returned to normal activity. Pulmonary function testing done seven years after exposure indicated that lung damage was still present in all four workers and had probably originated at the time of the accident (Hardy, et al. 1972). Two additional cases of mortality following acute acrylonitrile exposure have been reported. Both involved children, one treated with acrylonitrile for scalp lice and the other sleeping in a room fumigated with acrylonitrile (Grunske, 1949).

Toxicological studies give no clear insight into the possible mechanisms of acute and subacute acrylonitrile toxicity. Although Tarkowski (1968) proposed some evidence favoring a cyanide-mediated effect, there is also evidence against it (Paulet, et al. 1966). Earlier reports indicated that cyanide liberation is responsible for acrylonitrile toxicity (Desgrez, 1911 and Wagner-Jauregg, et al. 1948). Mediation of acrylonitrile toxicity by cyanide was considered because of the following observations noted upon acrylonitrile administration: (a) increased blood and urine thiocyanate concentration (Mallette, 1943; Wilson, et al. 1948; Lawton, et al. 1943); (b) appearance of free cyanide a cyanomethemoglobin in blood (Hashimoto and Kanai, 1965; Brieger, et al. 1952); (c) slight similarities to the toxicity symptoms and histopathologic results produced by administration of hydrocyanic acid and its salts; (d) successful use of some cyanide antidotes in treatment of some toxic symptoms resulting from acrylonitrile administration (Dudley, et al. 1942; Hashimoto and Kanai, 1965; Levina, 1951; Yoshikawa, 1968). Other hypotheses have attributed the toxicity of acrylonitrile to the intact molecule (Schwanecke, 1966; Paulet, et al. 1966; Ghiringhelli, 1954; Desgrez, 1911; Graham, 1965; Magos, 1962; Benes and Cerna, 1959). Support for these hypotheses comes from the following observations: (a) no correlation between acrylonitrile toxicity in guinea pigs or rats with either blood levels of cyanide ions and cyanomethemoglobin or the amount of thiocyanate excreted in urine (Ghiringhelli, 1954 and 1956; Magos, 1962); (b) no free cyanide ions detected in the blood of guinea pigs exposed to acrylonitrile (Dudley and Neal, 1942 and Dudley, et al. 1942); (c) histopathologic aberrations after acrylonitrile exposure not explicable as cyanide action (Dudley, et al. 1942; Benes and Cerna, 1959); (d) controversial reports on the action of specific cyanide antidotes, e.g., hydroxycobalamine, sodium nitrites and sodium thiosulfate in treatment of acrylonitrile poisoning (McOmie, 1943; Ghiringhelli, 1954; Magos, 1962; Hashimoto and Kanai, 1965).

Benes and Cerna (1959) postulated that in acrylonitrile sensitive animal species, quick decomposition of the entire acrylonitrile molecule to cyanide ion takes place and a typical cyanide toxicity is produced. However, Brieger, et al. (1952) reported that high SCN/CN ratios were observed in acrylonitrile sensitive animals.

Paulet, et al. (1966) reported that the toxic action of acrylonitrile in rabbits and guinea pigs is only partially due to cyanide liberation. It has been suggested that additional biotransformation may contribute partially to acrylonitrile's acute toxicity (Paulet, et al. 1966; Benes and Cerna, 1959). Desgrez (1911) in his earlier studies suggested a role for the conjugated double bond in acrylonitrile toxicity.

A number of other hypotheses have been developed to describe the mechanism of acrylonitrile toxicity (Hashimoto and Kanai, 1965; Ghiringhelli, 1954; and Magos, 1962). They suggest the blocking by cyanoethylation of important sulfhydryl group containing enzymes. This hypothesis was supported by the excellent antidotal action of cysteine and glutathione in guinea pigs and mice (Paulet, 1966; McLaughlin, et al. 1976). A general blocking effect upon cell metabolism together with irreversible inhibition of the respiratory enzymes have also been described as possible mechanisms of acrylonitrile toxicity (Ghiringhelli, 1954 and 1956). Acrylonitrile is known to deplete hepatic glutathione (Szabo, 1977). Dinu (1976) suggested that a decrease in hepatic glutathione levels renders the glutathione peroxidase ineffective, and the resulting increase in the peroxide levels damages the hepatic cells.

Synergism and/or Antagonism

Standard antidotes against cyanide poisoning have been used in attempts to abate the acute toxicity of acrylonitrile. Dudley and Neal (1942) found that neither sodium thiosulfate nor methylene blue afforded any protection against acrylonitrile lethality, while injection of sodium nitrite had a protective and antidotal action against the severity of symptoms (particularly the respiratory distress) and the lethality if given immediately before or after acrylonitrile exposure. This protective and antidotal action was observed for dogs, rats and rabbits but not for guinea pigs. Ghiringhelli (1954) found that guinea pigs were not protected against acrylonitrile toxicity by the anticyanide treatments tested: glucose, sodium thiosulfate and nitrite. Using another antidote for cyanide poisoning, hydroxycobalamin, Graham (1965) found that prior treatment of mice or dogs reduced the immediate (2 hours) lethality of acrylonitrile but increased the lethality at 24 hours. McLaughlin, et al. (1976) found that the combination of sodium nitrite with sodium thiosulfate was not effective against acrylonitrile lethality for mice, dogs and rats and only moderately effective in rabbits, while sodium thiosulfate alone was very effective rats and less effective for rabbits. Cysteine hydrochloride was the most effective of all antidotes against acrylonitrile lethality in all species tested by McLaughlin, et al. (1976).

Other kinds of treatments have been reported to affect the acute toxicity of acrylonitrile. Jaeger, et al. (1974) reported that acrylonitrile's LC50 for fasted rats was approximately three times lower than that for fed rats (150 vs 425 ppm x 4 hours). Szabo and Selye (1972) reported phenobarbital pretreatment diminished the acute adrenal apoplexy caused by acrylonitrile, and Paulet, et al. (1966) reported the same treatment delayed its lethality. HCN and CO were found to enhance acrylonitrile toxicity in experimental animals (Yamamoto, 1976) as well as in workers engaged in the acrylonitrile production (Ostarovskaya, et al. 1976).

Teratogenicity

Murray, et al. (1976) reported that their studies on Sprague-Dawley rats demonstrated a potential for acrylonitrile to cause fetal malformation when it was given to pregnant rats by gavage at high dose levels (65 mg/kg/day or approaching the LD50) on gestational days 6-15. Though sialodacryoadenovirus infection (murine mumps) occurred in both experimental and control animals, it is unlikely that this had an effect on the teratogenicity findings. At administration of 65 mg acrylonitrile/kg/day Murray, et al. (1976) found significant maternal toxicity and increased fetal malformations, including acaudea, short-tail, short trunk, missing vertebrae, and right-sided aortic arch. Other signs of embryo toxicity or fetotoxicity at this dose level were: increased frequency of early resorption sites (as detected by sodium sulfide stain), decreased fetal body weight and crown-rump length, and increased incidences of minor skeletal variants. At the time of Cesarean section, observations were made which are included in Table 5. The apparent pregnancy rate, i.e., the proportion of bred rats with visible implantation sites at the time of Cesarean section was significantly lower among rats given 65 mg acrylonitrile/kg/day than among the control rats. Administration of acrylonitrile had no significant effect on the litter size, the fetal sex ratio or the incidence or distribution of resorptions. At 65 mg/kg/day, the fetal body and crown-rump length were significantly lower than control values. No statistically significant effect was observed at the doses 10 and 25 mg/kg/day.

In Table 6 the incidence of external or soft tissue alterations among litters of rats given various doses of acrylonitrile by gavage is indicated. At 65 mg/kg/day the frequency of acaudate fetuses among litters was significantly higher than the control incidence. Also at this dose level, a statistically significant increase in the combined incidence of acaudate and short-tailed fetuses was observed. There were no statistically significant differences in the frequency of either of these tail anomalies alone or combined among litters of rats given the lower doses levels (10 or 25 mg/kg/day).

The soft tissue examination indicated right-side aortic arch in single fetuses at both 25 and 65 mg/kg/day (Table 7).

The incidence of skeletal alterations among litters of rats given acrylonitrile by gavage is summarized in Table 8. The incidence of skeletal alterations among litters of rats receiving 10 or 25 mg acrylonitrile/kg/day were

TABLE 6

Observations Made at the Time of Cesarean Section of Rats Receiving Acrylonitrile by Gavage
Murray, et al. 1976

	Dose Level of Acrylonitrile, mg/kg/day[a]			
	0	10	25	65
Number of bred females	43	39	33	29
Number of deaths/no. of females	0/43	0/39	0/33	1/29
Apparent pregnancy rate[b]	88% (38/43)	90% (35/39)	89% (29/33)	69% (20/29)[c,
Total pregnancy rate[e]	88% (38/43)	90% (35/39)	89% (29/33)	83% (24/29)
Proportion of pregnant animals detected only by sulfide staining[f]	(0/38)	(0/35)	(0/29)	17% (4/24)[d]
Number of litters	38	35	29	18
Implantation sites/dam[g, h]	12±3	12±3	11±4	12±3
Live fetuses/litter[g,h]	12±3	11±3	11±4	12±3
Resorptions/litter[g,h]	0.7±0.9	0.6±0.8	0.4±0.6	0.6±0.7
% Implantations resorbed[h]	6% (26/469)	5% (21/409)	3% (11/323)	4% (10/222)
Litters with resorptions[h]	47% (18/38)	40% (14/35)	34% (10/29)	44% (8/18)
Litters totally resorbed[h]	0	0	0	1
Resorptions/litters with resorptions[h]	1.4(26/18)	1.5(21/14)	1.1(11/10)	1.2(10/8)
Sex ratio, M:F	49:51	49:51	48:52	53:47
Fetal body weight, g[i]	5.68±0.28	5.78±0.25	5.80±0.33	5.26±0.32[j]
Fetal crown-rump length, mm[i]	44.4±1.0	44.5±1.3	45.0±1.2	43.6±1.2[j]

TABLE 6 (Continued)

LEGEND

[a] Acrylonitrile was given by gavage on days 6-15 of gestation.

[b] No. of females with visible implantation sites at the time of cesarean section or necropsy/total no. of bred females.

[c] A female which delivered her litter on day 20 of gestation was included in the calculation of the pregnancy rates. The litter was not examined for fetal alterations.

[d] Significantly different from control by Fisher's exact probability test, p 0.05.

[e] No. of females with implantation sites as observed either visually at the time of cesarean section or after staining the uterus with sodium sulfide stain/total no. of bred females.

[f] No. of females with implantation sites detected only after staining the uterus with sodium sulfide stain/total no. of females with implantation sites.

[g] Mean ± S.D.

[h] Data from the four females in which implantation sites were detected only after sodium sulfide staining of the uterus were not included in these calculations.

[i] Mean of litter means ± S.D.

[j] Significantly different from control mean by Dunnett's test, p 0.05.

TABLE 7

Incidence of Fetal Alterations Observed During the External or Soft Tissue Examination Among Litter of Rats Receiving Acrylonitrile by Gavage, Murray, et al. 1976

		Dose Level of Acrylonitrile, mg/kg/day[a]			
		0	10	25	65
		No. Fetuses/No. Litters Examined			
EXTERNAL EXAMINATION		443/38	388/35	312/29	212/17
SOFT TISSUE EXAMINATION		154/38	135/35	111/29	71/17
EXTERNAL EXAMINATION		% Affected (No. Affected)			
Acaudate	F[b]	0	0	0.6(2)	2(4)[c]
Acaudate or short tail	F	0.2(1)	0	0.6(2)	4(8)[c]
	L	3(1)	0	7(2)	35(6)
Short trunk	F	0	0	0	1(3)[c,d]
	L	0	0	0	18(3)
Imperforate anus	F	0	0	0	1(2)[d]
	L	0	0	0	12(2)
SOFT TISSUE EXAMINATION					
Right-sided aortic arch	F	0	0	1(1)	1(1)[d]
	L	0	0	3(1)	6(1)
Ovaries, anteriorly displaced	F	0	0	1(1)[d]	1(1)[d]
	L	0	0	3(1)	6(1)
Missing kidney, unilateral	F	1(1)	0	0	1(1)[d]
	L	3(1)	0	0	6(1)
Dilated renal pelvis, unilateral	F		0	0	2(2)
	L	0	0	7(2)	0
Dilated ureter, left	F	0	0	1(1)	1(1)[d]
	L	0	0	3(1)	6(1)

TABLE 7 (Continued)

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[a] Acrylonitrile was given by gavage on days 6-15 of gestation.

[b] F = fetuses; L = litters.

[c] Significantly different from control by a modified Wilcoxon test, p 0.05.

[d] This alteration occurred only in fetuses with a short or missing tail at this dose level.

TABLE 8

Incidence of Skeletal Alterations Among Litters of Rats Receiving Acrylonitrile by Gavage
Murray, et al. 1976

		Dose Level of Acrylonitrile, mg/kg/day^{a}			
		0	10	25	65
		No. Fetuses/No. Litters Examined			
SKELETAL EXAMINATION		443/38	388/35	312/29	212/17
SKULL BONE EXAMINATION		289/37	253/34	201/24	141/17
SKELETAL EXAMINATION		% Affected (No. Affected)			
Vertebrae - 12 thoracic and 5 lumbar (normal no. is 13 T and 6 L)	F^{b}	2(7)	0	2(7)	0
	L	3(1)	0	7(2)	0
-missing vertebrae other than 1 thoracic and 1^{c} lumbar^{c}	F	0.2(1)^{d}	0	0.6(2)^{d}	4(8)^{d,e,}
	L	3(1)	0	7(2)	35(6)
-missing centra of cervical vertebrae (other than C_1 and C_2)	F	5(23)	8(30)	10(31)	34(71)^{e}
	L	29(11)	46(6)	46(13)	88(15)
Ribs -missing 13th pair only	F	2(7)	0	2(7)	0
	L	3(1)	0	7(2)	0
-missing more than 1 pair^{g}	F	0	0	1(2)^{d}	2(4)^{d,e}
	L	0	0	7(2)	24(4)

TABLE 8 (Continued)

		Dose Level of Acrylonitrile, mg/kg/day[a]			
		0	10	25	65
Sternebrae - delated ossification, 5th	F	2(9)	3(13)	4(13)	15(31)[e]
	L	16(6)	23(8)	34(10)	59(10)
-missing, 5th	F	0	0	1(2)	1(2)
	L	0	0	7(2)	12(2)
-split, 5th	F	1(4)	1(3)	1(3)	4(8)
	L	10(4)	9(3)	10(3)	30(5)
-split, 2nd	F	0	0	0	2(4)[e]
	L	0	0	0	24(4)
SKULL BONE EXAMINATION					
-delayed ossification any skull bone	F	7(21)	6(15)	6(12)	4(5)
	L	30(11)	26(9)	29(7)	18(3)

[a] Acrylonitrile was given by gavage on days 6-15 of gestation.

[b] F - fetuses; L - litters.

[c] The actual number of thoracic, lumbar and sacral vertebrae of each of the affected fetuses were as follows (normal no. is 13 T, 6 L, 4 S): Control - 12T, 2L, OS; 25 mg/kg/day - 2T, OL, OS, 2T, 1L, 1S; 65 mg/kg/day -13T, 3L, OS; 3T, OL,)S; 13T, 6L, 2S; 7T, 3L, OS; 13T, 3L, OS; 2T, OL, OS; 3T, OL, OS; 13T, 5L, 4S.

[d] This alteration occurred only among fetuses with short or missing tail at this dose level.

[e] Significantly different from control by a modified Wilcoxon test, p 0.05.

[f] This alteration occurred only among fetuses with 12 thoracic and 5 lumbar vertebrae.

[g] The affected fetuses exhibited 0-7 pairs of ribs (normal no. is 13).

not significantly different from control litters. At 65 mg/kg/day, a significant increase was seen in the frequency of fetuses missing vertebra(e) other than a single thoracic and single lumbar vertebra. Also at this dose, each acaudate or short-tailed fetus (and only these fetuses) had this defect, ranging in severity from missing a single lumbar vertebra to missing 12 thoracic, all lumbar and all sacral vertebra. In addition, the incidence of fetuses missing more than one pair of ribs was significantly higher than control litters (Table 9).

An additional study by Murray, et al. (1978) concluded that when Sprague-Dawley rats were exposed to 0, 40, or 80 ppm of acrylonitrile by inhalation, teratogenic effects in the offspring of pregnant rats were suggested at 80 ppm but not 40 ppm. Significant maternal toxicity was found at both 80 and 40 ppm.

A second generation progress report from Litton Bionetics to MCA (Beliles, et al. 1977) summarizes results of a three generation reproduction study of rats receiving acrylonitrile in drinking water. Based on the F_0 and F_1 generations the authors conclude the followings:

1. Acrylonitrile at 500 ppm reduced body weight gain and food intake of the first generation parent rats (F_o);
2. At 100 and 500 ppm water consumption was reduced in F_o rats;

TABLE 9

Status Report (13 Months) on 2-Year Study Incorporating Acrylonitrile in the Drinking Water of Rats, Norris, 1977 - Observation of Palpable Masses in Mammary Gland Region[a] - Norris, 1977

	MALES			TOTAL		FEMALES			TOTAL	
	A[b]	B[c]	C[d]	No.	%	A	B	C	No.	%
CONTROLS	4/73[e]	0/10	1/7	5/90	5.5	12/79	2/10	0/1	14/90	15.5
35 PPM	0/44	0/10	0/3	0/57	0/0	11/45	0/10	3/4	14/59	23.7
100 PPM	3/46	0/10	1/1	4/57	7.0	9/42	3/10	3/5	15/57	26.3
300 PPM	3/41	0/10	0/7	3/58	5.2	11/32	1/10	8/15	20/57	35.1

[a] Norris, 1977

[b] A - Alive at 13 months (12/21/76).

[c] B - Interim sacrifice animals after 12 months on study.

[d] C - Dead at 13 months (12/21/76).

[e] No. mass bearing animals/No. animals in group A, B, or C.

3. At 500 ppm the pup survival in both matings of the first generation was reduced. Reducing the litters and fostering the pups onto untreated mothers lessened mortality of the pups, suggesting a maternal effect;
4. In the second generation the body weights (500 ppm) of the pups at day 21 of lactation were reduced at both matings;
5. Gross observations, as yet unconfirmed by histopathologic evaluation, suggested a tumorigenic effect in female rats held 20 weeks after the second litter (about 8 months of age); and
6. The survival of the pups at the 100 ppm concentration was reduced in one mating of each generation; because of this inconsistency the toxicologic significance has not yet been assessed.

Recent verbal communication from Beliles provided further expansion on the findings of this ongoing study: The effects seen at 500 ppm are quite consistent and responsible with respect to prenatal viability of the pups. Most of the delerious effects on the pups appear in late lactation, which may be due either to maternal/toxic phenomena, or to insufficient fluid intake by the lactating mothers.

Beliles verbally confirmed significant tumorigenic effects in the dams. The verified occurrence of zymbal gland carcinomas were seen as in other studies (see Carcenogensis; Norris, 1977; Quast, et al. 1977). Only partial histopathology is available at this time, final report on the whole study is anticipated early 1979.

Mutagenicity

The mutagenicity of acrylonitrile to various organisms has been described by several investigators. Behes and Aram (1969) noted only weak effects in Drosophila melanogaster and concluded that acrylonitrile toxicity towards the species limited the testing. Milvy and Wolff, (1977) reported that in various strains of Salmonella typhimurium activated by mouse liver homogenate, acrylonitrile is mutagenic in the TA 1535 tester strain that is sensitive to base substitution, as well as strains TA 1538 and TA 1978, which are sensitive to frameshift mutagens. No dose-response data were obtained, however, and high reversion rates were seen in the controls. Milvy and Wolff reported that the presence of the activating system and NADPH cofactor is a prerequisite for acrylonitrile-induced mutagenesis (Milvy and Wolff, 1977).

In a comprehensive study Venitt, et al. (1977) concluded that acrylonitrile is a mutagen for Excherichia coli strains WP2, WP2 uvrA, and WP2 urvApolA. Acrylonitrile caused a slight dose-related increase in the number of revertant colonies compared with untreated bacteria in three of the four strains. WP2 lexA was not detectably reverted by acrylonitrile. Of the three strains showing a statistically significant mutagenic response, WP2 was slightly more sensitive to the mutagenic effect of acrylonitrile, showing a 4-fold increase over the spontaneous levels compared with a 3-fold increase for WP2 uvrA and a 2-fold increase for WP2 uvrApolA. Doses above 150 umol per plate caused a decline in mutagenic response, concomitant with increasing toxicity as shown by a dose-related reduction in the density of the bacterial lawn. An important observation reported by Venitt, et al. (1977) was that the addition of a mixed function metabolizing system in vitro (S-9 mixture prepared from the liver of Aroclor 1254-induced CB hooded male rats) had no detectable effect on the mutagenic action of acrylonitrile. Therefore, they concluded that acrylonitrile is a directly acting mutagen in these strains of E. coli.

The differential response of the tested strains to the mutagenic action of acrylonitile suggests that acrylonitrile causes non-excisable DNA damage. (Venitt, et al. 1977 and Green and Moriell, et al. 1976). Acrylonitrile has been shown to cyanoethylate ring nitrogen atoms of certain minor tRNA nucleosides and ribothymidine and thymidine (Ofengand, 1971 and 1976). Accordingly, Venitt, et al. (1977) suggested that acrylonitrile might react with thymine residues in DNA.

Carcinogenicity

The most pertinent animal carcinogenesis studies are two studies conducted by the Dow Chemical Company, Toxicology Research Laboratory, Midland, Michigan under the administration of The Manufacturing Chemists Association. Both studies are 2-year studies concerned with long-term effects of acrylonitrile in the drinking water of rats. The following discussion of the first study (Norris, 1977) is based on a 13-month interim report. Discussion of the second study (Quast, et al. 1977) is based on a 12-month interim report. (Updated data were not accessible at the time of this document's preparation, but will be available for subsequent iterations).

In both studies, concentrations of acrylonitrile in the drinking water of the rats were 0, 35, 100 and 300 mg/l. The concentrations were equivalent to daily dosages of approximately 4, 10, and 30 mg/kg body weight, respectively. The Quast, et al. (1977) study used Sprague-Dawley rats, spartan substrain, while the Norris study did not explicitly mention the strain of rat employed. Both studies utilized both males and females.

Norris (1977) noted a statistically significant dose-related decrease in water consumption by the rats at all concentrations of acrylonitrile, as well as lowered food consumption by rats at the highest concentration and lowered food consumption by the female rats at the intermediate concentration. The decreased food and water consumption resulted in a statistically significant decrease in body weight of animals at the two higher concentrations (100 and 300 mg/l). The body weight of the animals at the lowest concentration was also decreased, although not by a statistically significant amount when compared with controls. Urinalysis showed an increase in specific gravity in the urine of rats of both sexes at the 300 mg/l concentration throughout the study and in the females at the 100 mg/l concentration in the 12th month of the study. The effect is probably due to lower water intake. As of 13 months, there was a higher incidence of a) subcutaneous masses in the mammary region of females at all concentrations of acrylonitrile (Table 8) b) masses of the ear canal among both sexes at the highest concentration and in females only at the intermediate concentration (Table 10) c) proliferative lesions of the brain at the highest and next to higher concentration in males only (Norris, 1977).

Gross pathologic examination of some of the rats that died spontaneously and of those rats that were sacrificed after one year of administration of acrylonitrile displayed focal areas of hyperplasia and/or polyp formation in the non-glandular portion of the stomach of several animals at the two higher concentrations. At the lowest concentration no gross pathologic changes were observed in the stomachs of the rats.

Upon microscopic examination of the brains of animals sacrificed at the 12-month interim kill, proliferative lesions were observed in rats on the 300 and 100 ppm concentrations. These lesions were not observed on gross examination. A similar lesion was noted in the spinal cord of one rat on the 100 ppm concentration (Table 10). A summary of the findings of the 13-month interim report of Norris (1977) appears in Table 11.

Quast, et al. (1977) obtained data on appearance, demeanor, body weights, food and water consumption, routine hematology, clinical chemistry determinations (serum urea, alkaline, phosphatase and SGPT activity), routine urinalysis, organ weights, organ-to-body weight ratios, and gross and microscopic pathologic examination of tissues.

TABLE 10

Status Report (13 Months) on 2-Year Study Incorporating Acrylonitrile in the Drinking Water of Rats, Norris, 1977 - Ear Canal Masses -[a] Norris, 1977

	MALES			TOTAL		FEMALES			TOTAL	
	A[b]	B[c]	C[d]	No.	%	A	B	C	No.	%
CONTROLS	1/73[e]	0/10	0/7	1/90	1.1	1/79	0/10	0/1	1/90	1.1
35 PPM	1/44	0/10	0/3	1/57	1.7	0/45	0/10	0/4	0/59	0
100 PPM	0/46	0/10	0/1	0/57	0	0/42	2/10	1/5	3/57	5.3
300 PPM	4/41	1/10	1/7	6/58	10.3	4/32	1/10	4/15	9/57	15.8

[a] Norris, 1977

[b] A - Alive at 13 months (12/21/76).

[c] B - Interim sacrifice animals after 12 months on study.

[d] C - Dead at 13 months (12/21/76).

[e] No. mass bearing animals/No. animals in group A, B, or C.

TABLE 11

Status Report (13 Months) on 2-Year Study Incorporating Acrylonitrile (AN) in the Drinking Water of Rats - Proliferative Lesions[a] in Brain of Rats Sacrificed After 12 Months -

CONCENTRATION OF ARCYLONITRILE IN DRINKING WATER (PPM)	MALES	FEMALES	
CONTROL	0/10	0/10	
35	0/10	0/10	
100	0/10	3/10	(Plus 1 spinal cord lesion)
300	1/10	2/10	

[a] Not Observed Grossly.

Rats ingesting 100 or 300 mg/l of acrylonitrile showed a poorer overall body condition, being smaller and having an unthrifty condition. In these two treatment groups, a greater number of rats, compared with the controls either died or were selected for autopsy, assumedly because they were moribund or had palpable tumors, prior to the scheduled 12-month sacrifice. This was particularly true in female rats ingesting 300 mg/l acrylonitrile where 4 out of the 10 rats were selected for autopsy prior to the 12-month scheduled sacrifice. In all treatment groups, there was a dose-related decrease in water consumption, food consumption and body weight gains. Approximate amounts of acrylonitrile ingested by rats at the three concentrations were computed to be 4, 10 or 30 mg acrylonitrile/kg/day. Increased specific gravity of urine was observed in males and females ingesting 300 mg/l acrylonitrile and in females ingesting 100 mg/l acrylonitrile. The 300 mg/l group of females showed an elevated serum alkaline phosphatase activity.

Gross and microscopic pathologic changes of both a nontumorous and tumorous nature were detected with greater frequency in rats in the 100 and 300 mg/l acrylonitrile groups than in the 35 mg/l and control groups. There was an increased occurrence of tumors in the stomach, nervous system, and zymbal gland of the ear canal region in rats ingesting 100 or 300 mg acrylonitrile/l compared with the control and 35 mg/l groups. These tumors are considered treatment-related. Other types of tumors also occurred more frequently in these rats than in controls, but their relationship to treatment is uncertain due to their low

TABLE 12

Status Report on 2-Year Study Incorporating Acrylonitrile in the Drinking Water of Rats - Summary of Findings as of 13 Months -

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Statistically significant decreased water consumption at all dose levels.

Decreased food consumption at 300 ppm in males and females and at 100 ppm in females.

Statistically significant decreased body weights of males and females at 300 and 100 ppm and a nonstatistically significant decrease at 35 ppm.

Increased specific gravity of urine of males and females at 300 ppm and in females at 100 ppm.

Increased incidence of masses in the mammary region in females at all dose levels.

Polyps in stomach of some male and females at 300 ppm and females at 100 ppm.

Increased incidence of ear canal masses in males and females at 300 ppm and in females at 100 ppm.

Proliferative lesions in central nervous system of males and females sacrificed after 12 months at 300 and 100 ppm.

Increased mortality among females at 300 ppm.

incidence and the small size of the groups. Marked nontumorous morphologic changes reflecting toxicity were detected in various organs in rats ingesting 100 or 300 mg/l. Significant increases were observed in the organ weight/body weight ratio of heart, liver, and brain. Also, the relative brain weight:body weight ratio was increased in male rats receiving 100 mg acrylonitrile/l. Relative liver and kidney weight; body weight ratios were significantly increased in female rats at the 300 mg/l dose. The absolute and relative organ weight changes in male and female rats were associated with decreased fasting body weights.

To summarize the study of Quast, et al. (1977), male and female rats maintained on water containing 35 mg acrylonitrile/l for 12 months exhibited signs of toxicity characterized by slightly decreased water and food consumption and body weight gain, without a noticeable tumorigenic response. When the dose was increased to 100 or 300 mg acrylonitrile/l in drinking water, the rats showed marked signs of toxicity in addition to a tumorigenic response involving stomach, nervous sytem, and Zymbal gland of the ear canal. (Tables 13 and 14). It should be noted that zymbal gland tumors were also verbally reported by Beliles (personal communication) to be present in rats during a 3 year reproductive study (Beliles, Murray 1977) (see section or Teratology).

In further support of the above data, a letter transmitted by the Manufacturing Chemists Association dated February 22, 1978, includes a summary of preliminary findings of a study by Dow Chemical U.S.A. indicating a higher incidence of brain tumors at 80 and 20 ppm in drinking water when compared to historic control data.

TABLE 13

Results of Histopathologic Examination of Tumorous Changes in Male Rats Maintained on Water Containing Acrylonitrile for 12 Months[a]

Microscopic Findings	Concentration of acrylonitrile in the water (ppm)[b]			
	0	35	100	300
Number of rats in the group	10	10	10	10
Kidney				
Hemangioma - unilateral	0	0	1	0
Stomach				
Focal squamous cell papilloma(s)	0	0	1	7
Central nervous system				
Microtumor suggestive of mesodermal origin	0	0	2	1
Histopathologic diagnosis of the following tumors based upon those grossly recognized at autopsy.				
Small intestine				
Mucinous cystadenocarcinoma without metastasis	0	0	1	0
Large intestine				
Well-differentiated polyploid adenocarcinoma without metastasis	0	0	0	1
Ear canal tumor				
Zymbal gland carcionoma without metastasis	0	0	0	1
Total number of tumors	0	0	5	10

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[a] Quast, et al. 1977

[b] Data are listed as number of rats affected in the group.

TABLE 14

Results of Histopathologic Examination of Tumorous Changes in Female Rats Maintained on Water Containing AN for 12 Months[a]

Microscopic Findings	Concentration of acrylonitrile in the water (ppm)[b]			
	0	35	100	300
Number of rats in the group	9	9	10	10
Stomach				
Focal squamous cell papilloma(s)	0	0	0	5
Central nervous system				
Microtumor suggestive of mesodermal origin	0	0	4	2
Histopathologic diagnosis of the following tumors based upon those grossly recognized at autopsy.				
Pituitary gland				
Adenoma	1	0	0	0
Ear canal tumor				
Zymbal gland carcinoma without metastasis	0	0	2	1
Subcutaneous tumor(s)				
Mammary gland adenocarcinoma without metastasis	2	0	1	0
Mammary gland adenocarcinoma with pulmonary metastasis	0	0	0	1
Mammary gland fibroadenoma				
One per rat with tumor	0	0	1	2
Three per rat with tumor	0	0	1(3)[c]	0
Uterus				
Endometrial polyp	2	0	2	1
Leiomyoma	0	0	0	1
Uterocervix fibroma	0	1	12	1
Total number of tumors	5	1	14	14

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[a] Quast, et al. 1977

[b] Data are listed as number of rats affected in the group.

[c] A single rat in this group had 3 mammary gland fibroadenomas.

Maltoni, et al. (1977) have recently reported the results of long-term carcinogenicity bioassays of acrylonitrile, lasting more than 130 weeks. The monomer has been tested in Sprague-Dawley rats by inhalation (40, 20, 10, and 5 ppm, 4 hours daily, 5 times weekly for 52 weeks) and by ingestion (5 mg/kg body weight in olive oil by stomach tube, once daily, 3 times weekly for 52 weeks). A slight enhancement of the incidence of some tumors has been reported -- mammary tumors, fore-stomach papillomas and acanthomas, skin carcinomas, and encephalic tumors, particularly gliomas.

It should be noted that only one dose was used in the ingestion studies, so that no-dose response relationship could be obtained. Data from the inhalation studies are presented on mammary tumors and Zymbal gland carcinomas and on encephalic tumors (particularly gliomas), uterine carcinomas and others (Table 15).

As an additional note it should be pointed out that possible impurities found in the acrylonitrile used by various investigators might possibly affect the determination of carcinogenic effect. The role of these impurities has not yet been determined.

A recent preliminary epidemiological study from E. I. de Pont de Nemours and Company on its Camden, South Caroline textile fibers plant showed that persons exposed to acrylonitrile at the plant are at greater risk of developing cancer, as compared with company, national and regional experience (O'Berg, 1977). This preliminary retrospective study analyzes the cancer experience of the cohort of 1343

TABLE 15

Results of Inhalation Study by Maltoni, et al. 1977.

GROUPS No.	TREATMENT		ANIMALS (Sprague-Dawley rats, 12 weeks old at start)		Corrected number (a)	ANIMALS WITH TUMOURS														
						Mammary tumours												Zymbal gland carcinomas		
										Histotypes										
										Fibroadenomas and fibromas				Carcinomas						
	Dose	Length (weeks)	Sex	No. at start		No.	% (b)	Average latency time (weeks) (c)	Mean No. of tumours/animal	No.	% (b)	Average latency time (weeks) (c)	Mean No. of tumours/animal	No.	% (b)	Average latency time (weeks) (c)	Mean No. of tumours/animal	No.	% (b)	Average latency time (weeks) (c)
I	40 ppm	52	♀	30	30	7	23.3	89.4	1.4	5	16.6	94.4	1.4	2	6.6	77.0	1.5	-	-	-
			♂	30	30	4	13.3	112.5	1.0	3	10.0	130.7	1.0	1	3.3	58.0	1.0	-	-	-
			♀ and ♂	60	60	11	18.3	97.8	1.3	8	13.1	106.0	1.2	3	5.0	70.7	1.3	-	-	-
II	20 ppm	52	♀	30	30	10	33.3	107.4	1.0	9	30.0	110.7	1.0	1	3.3	76.0	1.0	1	3.3	77
			♂	30	30	4	13.3	41.5	1.0	2	6.6	48.0	1.0	2	6.6	35.0	1.0	-	-	-
			♀ and ♂	60	60	14	23.3	88.6	1.0	11	18.3	99.3	1.0	3	5.0	49.3	1.0	1	1.6	77
III	10 ppm	52	♀	30	30	7	23.3	102.3	1.4	7	23.3	102.3	1.4	-	-	-	-	1	3.3	101.0
			♂	30	30	1	3.3	114.0	1.0	1	3.3	114.0	1.0	-	-	-	-	1	3.3	104.0
			♀ and ♂	60	60	8	13.3	103.7	1.4	8	13.3	103.7	1.4	-	-	-	-	2	3.3	102.
IV	5 ppm	52	♀	30	30	10	33.3	92.2	1.2	6	20.0	93.0	1.3	4	13.3	91.0	1.0	-	-	-
			♂	30	30	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			♀ and ♂	60	60	10	16.6	92.2	1.2	6	10.0	93.0	1.3	4	6.6	91.0	1.0	-	-	-
V	None (Controls)		♀	30	30	5	16.6	94.0	1.0	4	13.3	93.0	1.0	1	3.3	98.0	1.0	-	-	-
			♂	30	30	1	3.3	135.0	1.0	-	-	-	-	1	3.3	135.0	1.0	-	-	-
			♀ and ♂	60	60	6	10.0	100.8	1.0	4	6.6	93.0	1.0	2	3.3	116.5	1.0	-	-	-
Total				300	300															

(a) Alive animals after 2 weeks, when the first tumour (a mammary carcinoma) was observed.
(b) The percentages are referred to the corrected number.
(c) The latency time of mammary tumours is given as age; the latency time of the other tumours is given as period from the start of the experiment.

workers who were exposed to acrylonitrile between 1950 and 1967. It considers no latency, 15-year latency and 20-year latency periods for cancer development. About 36 percent of the 1343 employees are presently lost to follow-up.

In this study, mortality rates were analyzed for active employees and retirees, and cancer diagnoses and deaths for active employees were analyzed using company and national referent rates to determine expected numbers. The most sensitive analysis, using du Pont referent rates (correcting for the "healthy worker effect") and a 20-year induction for cancer (which narrows down the cohort to 470) indicated eight observed deaths compared with 4.0 expected. The du Pont Registry data revealed 16 cases of cancer compared to 5.8 expected. The difference was found to be highly significant. (See Tables 16 and 17).

The author of the study notes that the results presented are preliminary, and that additional follow-up of persons who quit or were laid off is required. In the cohort, the losses to follow-up represent a significant percentage (36 percent). About one-third of the losses have had short-term exposure (less than six months). The acrylonitrile exposure levels were only qualitatively reported (on the basis of the job and its potential for exposure) as 3 (lowest exposure), 2 (moderate exposure) or 1 (highest exposure). Times at each level were estimated for each cancer mortality. Excess cancer was observed when considering all sites; individual sites with excess cancer mortality were lung, large intestine and possibly prostate. (See Tables 16 and 17). The excess cancer in the cohort is distributed among

TABLE 16

Observed and Expected Numbers of Cancer Deaths* for an Acrylonitrile Cohort with Six Months or Greater Exposure, Based on du Pont Company Rates for 196901975, 20-Year Latency (O'Berg, 1977)

	Male Wage			Male Salary	
	Observed	Expected	P-Value	Observed	Expected
All sites	7	3.2	0.04	1	0.6
Lung	4	1.2	0.03	0	0.2
Large Intestine	2	0.2		0	0.0
Prostate	1	0.1		0	0.0

TABLE 17

Observed and Expected Numbers of Cancer Cases* for an Cohort with Six Months or Greater Exposure, Based on du Pont Company Rates for 1969-1975, 20-Year Latency (O'Berg, 1977)

	Male Wage			Male Salary	
	Observed	Expected	P-Value	Observed	Expected
All sites	13	4.4	.0006	2	0.8
Lung	5	1.2	.008	1	0.2
Large Intestine	3	0.4	.008		0.1
Prostate	1	0.3			0.0

*Source: Cancer Registry Entries (active employees only).

many anatomical sites although lung and intestinal cancer predominate. Significant excess overall cancer mortality cannot be entirely attributable to these primary sites. Because an excess of lung cancer occurs in this cohort, cigarette smoking must be considered as a possible agent or cofactor; smoking histories were not available for this interim report however (O'Berg, 1977). Another consideration should also be mentioned; the du Pont cohort had in common exposure to the following chemicals besides acrylonitrile: dimethylformamide, hydrogen peroxide, hydroxyanisole, methyl acrylate, phenylether-biphenyl mixture, sodium metabisulfite, sulfur dioxide, sulfuric acid and titanium dioxide. (O'Berg, 1977 letter). A tabulated list of all cancer cases appear in Table 18 (O'Berg, 1977).

Monson (1977), analyzed the cancer mortality (and morbidity) experience of 355 white male United Rubber Workers Union members who had potential exposure to acrylonitrile in the polymerization recovery and laboratory areas of B.F. Goodrich plant #3, Akron (Table 19). The mortality experience of this cohort between 1-1-40 and 7-1-76 was compared to that of the U.S. general population. Person-years of follow-up were determined in 5-year age-time groupings and expected numbers were calculated by multiplying these person-years by age-time-cause specific mortality rates for U.S. white males. The cancer registries of the four Akron area hospitals were reviewed between 1964 and 1974.

Determination was also made of any B.F. Goodrich employee who developed cancer between these years. In addition, persons who had cancer as the secondary cause of death on the death certificate were identified. Based on these data,

TABLE 18

An Cohort Cancer Cases and/or Deaths, 1969-1975, Duration of Exposure (O'Berg, 1977)

Cancer Site	Date of First Exposure	Total Years of Exposure Rounded to Nearest Whole Year	Time at Severity 1	Time at Severity 2	Time at Severity 3
Lung	1950	26	18 gr.	8 yr.	
Lung	1950	20			20 yr.
Lung	1950	7	5 yr. 1 mo.	1 yr. 4 mo.	2 mo.
Lung	1950	4	1 yr. 2 mo.	1 yr. 2 mo.	2 yr. 1 mo.
Lung	1952	5	5 yr. 1 mo.		
Lung	1952	4	1 yr. 2 mo.		3 yr. 4 mo.
Large Intestine	1951	13			13 yr. 1 mo.
Large Intestine	1951	5	5 yr.		6 mo.
Large Intestine	1952	5	5 yr.		
Prostate	1950	14			13 yr. 9 mo.
Prostate	1952	5	5 yr. 3 mo.		
Lymphosarcoma	1951	1			4 mo.
Hodgkins	1951	13			12 yr. 9 mo.
Penis	1952	12		8 mo.	11 yr.
Thyroid	1952	14	2 yr. 8 mo.	1 yr. 8 mo.	10 yr.
Nasopharynx	1950	7			7 yr. 4 mo.
Bladder	1950	3	3 yr. 1 mo.		
Pancreas	1952	6	6 yr.		

*20-year latent period assumed.

TABLE 19

Observed and Expected Deaths for 355 White Male Union Members Who Ever Worked in Departments 5570 - 5579. Monson, 1977

ICD No. *	Cause of death	Observed	Expected	SMR**
	All causes	64	83.1	77
140-205	Malignant neoplasms	20	15.6	128
150-159	Digestive	4	4.6	88
153	Large intestine	1	1.3	74
160-164	Respiratory	9	5.2	175
177-181	Genitourinary	2	1.7	117
200-205	Lymphatic & Hematopoietic	3	1.6	186
-	Residual cancer	2	2.2	94
330-334	Cerebrovascular disease	5	5.1	97
400-468	Circulatory disease	22	37.5	59
470-527	Respiratory disease	5	4.3	117
530-581	Digestive disease	2	4.5	44
590-637	Genitourinary disease	1	1.3	77
800-999	External causes	5	8.8	57
-	Residual	4	10.5	38

* International Classification of Diseases. 7th Revision.

** Standardized Mortality Ratio: 100 x observed/expected.

Monson (1977) compared cancer morbidity rates in men who worked in departments with potential exposure to acrylonitrile with unexposed male workers.

Acccrding to this study Monson (1977) reported that among the male cohort who had some exposure to acrylonitrile as well as other chemical exposure in the cohort (such as butadrene), the most significant findings was an excess of lung cancer (9 observed, 5.2 expected). Among lymphatic and hematopoietic cancers there were 3 deaths where 1.6 expected. Monson (1977) reported that there were no excess deaths from cancer of the large intestine. He also reported that the excess of mortality due to cancer from all sites and of the lung were seen primarily in men who started working after 1939 and died after 1959 (Table 19). He reported that there were 6 men identified through the Akron tumor registries as having cancer; none of these men were known to be dead as of 7/1/76. The sites of the cancers of these 6 men were; large intestine (1), kidney (2), bladder (1), skin (1), lymphoma (1). He concluded that an excess of cancer as measured by mortality or morbidity occurred among men who had exposure to acrylonitrile. The excess was spread over a number of sites but was greatest for lung cancer. He indicated that he is unable to determine whether this excess represents a casual association with work in those departments in which potential exposure to acrylonitrile may occur from information currently available. He also indicated that the study is confounded by the fact that most of the acrylonitrile exposed workers developing cancer had worked in other departments where they were potentially exposed to other chemicals. Finally, Monson (1977) concluded that although proof does not exist that the current levels of acrylonitrile and other chemical exposures (such as butadien) are harmful, it would be prudent to reduce further exposure to the chemical. No quantitative exposures of acrylonitrile are listed in the report. Monson (1977) notes that his data at Goodrich conflicts with O'Berg's (1977) du Pont study in which an excess of intestinal cancer was observed. Aside from difference in other chemical exposures suffered by the two cohorts, Monson (1977) did not assume a 20 year latency period (providing greater sensitivity) while O'Berg (1977) did.

TABLE 20

Observed and Expected Deaths from all Cancers and Lung Cancer According to Selected Characteristics

Characteristic	Category (years)	All Cancers		Lung Cancer	
		Obs.	Exp.	Obs.	Exp.
Age started working*	35	5	4.9	2	1.2
	35-44	5	4.7	1	1.8
	45	10	6.0	6	1.8
Year started working	1940	0	0.6	0	0.2
	1940-49	12	7.9	3	2.3
	1950	8	7.1	6	2.3
Age at death	65	11	11.1	5	3.5
	65	9	4.5	4	1.3
Year of death	1960	3	2.6	0	0.6
	1960-69	9	6.2	4	1.9
	1970	8	6.8	5	2.3

* Age and year refer to entrance into 5570-5579.

CRITERION FORMULATION

Existing Guidelines and Standards

The Existing Standards for acrylonitrile in various countries and various years appear in Table 21.

It is evident that at this time, the Russian standard is substantially less (two order of magnitude) than the American and West European standards. The work of Scupakas (1968) indicates, however, that the standard may be exceeded significantly. The study of Orusev and Popovski (1973) of a Yugoslavian acrylic fiber plant indicated that their in-plant concentrations of acrylonitrile begin to approach the TLV in the U.S.A. Other investigators have noted that the air standards are often exceeded (Schwanecke, 1966; Thiede and Franzen, 1965; Babanov, 1960), although it is unlikely that higher concentrations occur throughout the day.

Almost twenty years ago, it was advocated by Elkins (1959) in the U.S.A. that the "MAC" be reduced to 10 ppm (corresponding to that of HCN). According to Babanov (1960) an acute danger exists even from 0.85-6.1 mg/m^3 (0.4 - 2.8 ppm) in working areas.

In January, 1978, the Occupational Safety and Health Administration (OSHA) announced an emergency temporary standard to reduce sharply worker exposure to acrylonitrile. OSHA director, Dr. Eula Bingham, said that, effective immediately, employee exposure to acrylonitrile must be reduced to 2 ppm averaged over an eight-hour period (TLV). Dr. Bingham noted that the Emergency Temporary Standard was necessary because of data from studies of workers previously

TABLE 21

Standards for Arcylonitrile Air Exposure Levels in Various Countries (between 1970-1974)

Year	Country	Air ppm	Standard mg/m^3	Kind of Standard	Reference
1970	U.S.S.R.	0.2	0.435	MAC ("Hygenic goal")	Grahl, 1970; Schwanecke, 1966; Babanov, 1960; Pokrokovsky, 1951; Thiede and Franzen, 1965
1970	Federal Republic of Germany	20.0	43.5	MAK	Grahl, 1970; Thiede and Franzen, 1965; Lefaux, 1966
1970	England	20.0	43.5	MAC	Grahl, 1970; Thiede and Franzen, 1965; Lefaux, 1966
1974	U.S.A.	20.0	43.5	TLV	Threshold Limit Values, 1974; Grahl, 1970; Mallette, 1943; Dudley and Neal, 1942; Stokinger, *et al*. 1963

exposed to acrylonitrile and laboratory tests, both of which established "exposure to acrylonitrile poses a potential carcinogenic risk to humans." While OSHA's position is that there is no way to determine a safe level of exposure to a carcinogen, in this case "a level was chosen to immediately minimize the hazard to the greatest extent possible within the confines of feasibility (Chemical and Engineering News, Jan. 23, 1978)."

The recent action of OSHA is, in fact, based upon studies done by the chemical industry itself. In March, 1977, the Manufacturing Chemists Association (MCA) reported interim results from a study of the chronic toxicity of acrylonitrile ingestion on rats. Findings were that ingestion of 100 and 300 ppm of acrylonitrile in drinking water produced tumors of the CNS and ear canal. In April, 1977, there were similar tumors reported among rats ingesting 35 ppm of the substance. (Norris, 1977). Confirming the laboratory results, du Pont informed OSHA of preliminary results of an epidemiological study of workers exposed to acrylonitrile at its textile fibers plant in Camden, S.C. (Chemical and Engineering News, Jan. 23, 1978; O'Berg, 1977). (See Human Carcinogenicity Studies under Effects).

Current Levels of Exposure

Indices of exposure, apart from very unspecific symptoms (such as spirographic examination of the lung) in the case of chronic exposure (Possner, 1965) include the determination of increased blood SCN^- level (Mallette, 1943; Wilson, et al. 1948; Lawton, et al. 1943) and elevated urinary SCN^- level (Mallette, 1943; Sax, 1957; Elkins, 1959; Lawton, et al. 1943).

It must be recognized that smoking presents a problem in ascertainment of occupational and other exposure because of the presence of nitriles in cigarette smoke. Thus, smokers may have a blood level of approximately 3 mg percent SCN^- in blood; the urinary SCN^- level of heavy smokers may normally reach 9 mg KSCN/l in contrast to a normal urinary level for non-smokers of 0.2 mg/l and for occasional smokers a normal urinary level of 1.2 mg KSCN/l (Elkins, 1959). Consequently, in testing for occupational or other exposure, if it is not known whether a person is a smoker, values of urinary KSCN _ 10 mg/l cannot be considered to result from occupational exposure. Sax (1957) suggests that it is advisable for the purposes of screening for exposure to have liver function tests if urinary analysis proves to be negative. In addition, another suggested method of screening is that of the spectrophotometric determination of cyanomethemoglobin in blood (Ullmanns, 1960; Magos, 1962).

The existing occupational standards have already been mentioned. It has also been noted that these standards are often exceeded. The production of significant amounts of acrylonitrile and HCN from thermal decomposition of polyacrylonitrile products has already been noted. For example, overheating of 1 kg of a polyacrylonitrile plastic about 15 g of HCN can be formed. Thus, the amont of HCN formed in a 30 m^3 room from 100-200 g of polyacrylonitrile fibers corresponds to 10-15 times the MAC values (Schwanecke, 1966; Thiede and Franzen, 1965; Mallette, 1943) and this underlines a special hazard of polyacrylonitrile plants. The possible synergism of acrylonitrile and HCN has already been alluded to.

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There are few data on monitoring of ambient air and drinking water levels of acrylonitrile. A notable exception is the analysis of in-plant air emission from a propylene-based acrylonitrile manufacturing plant by Hughes and Horn (1977). This lack of data prevents us from predicting most actual exposures of the public except for certain groups at high risk such as occupational workers. At the present, Emergency Air Standard, 2 ppm of acrylonitrile = 4.35 mg/m^3/day, the acrylonitrile intake of a worker at threshold level = 0.90 (4.35 mg/m^3) (20 m^3/day) = 78.3 mg/day, where 0.90 is the average retention of acrylonitrile (Young, et al. 1977). Thus, depending on the half-life of acrylonitrile, a substantial body burden in occupationally exposed individuals can result.

As indicated under Sources of Exposure, some additional environmental monitoring data is becoming available (Midwest Research Institute, 1977 and 1978). However, to data this information is preliminary in nature and conclusions on possible human exposures cannot be drawn.

Other groups at risk are listed in the next section. Due to a lack of data, it is impossible to calculate the actual intakes of acrylonitrile for these groups.

Special Groups at Risk

Shown below are various groups at varying degrees of risk to acrylonitrile exposure, with attached references, wherever feasible. It should be recalled that NIOSH has estimated that at least 125,000 individuals are exposed occupationally (NIOSH, 1977).

Occupational	(NIOSH, 1977)
1. Plastic	
Acrylonitrile Manufacturers	(NIOSH, 1977)
Polymer Manufacturers	(NIOSH, 1977)
Polymer Molders	(Scupakas, 1968)
Polymer Combustion Workers	(Rumberg, 1971; Duvall and Rubey, 1973)
Furniture Makers	(Vol'skii, et al. 1973)
2. Fabrics	(Rapaport, et al. 1974)
Fiber Manufacturers	(Orusev and Popovski, 1973; Valic and Zuskin, 1977)
Clothing Sewers	(Fedorchuk, 1973)
3. Biological Product Manufacturing	
Dental Polymer Manufacturers	(Crapper, et al. 1978)
Contact Lens Fabricators	(Stoy, et al. 1976)
Blood Filter Fabricators	(Lindsay, et al. 1977)
4. Water Treatment and Manufacturers	(Sato, et al. 1977)
5. Pesticide and Fumigant	
Manufacturers	(Radimer, et al. 1974)
Sprayers	(Radimer, et al. 1974)
Farmers	(Radimer, et al. 1974)

Non-Occupational

1. Accidental

Exposure to Liquid from Transportational spill	(Hardy, et al. 1972)
Combustion and Fire (firemen and domestic personnel)	(Duvall and Rubey, 1973; Michal, 1976; Hilado, et al. 1977)
Ingestion of Contaminated Water or Food	(Chudy and Crosby, 1978; Vettorazzi, 1977)
Respirations of Contaminated Air (environmental exposure to acrylonitrile or polyacrylonitrile plants)	

2. Non-accidental

Cigarette smokers	(Izard and Testa, 1968)
Wearers of acrylic dentures	(Crapper, et al. 1978)
Wearers of acrylic underwear, diapers, and sanitary napkins	(Rapoport, et al. 1974; Harada and Shimodi, 1975)
Ingestion of food wrapped in polyacrylonitrile wrapping	(Federal Register, 1974, 1975, 1976)
Exposure to acrylonitrile vapors from polyacrylonitrile furniture.	(Vol'skii, et al. 1973)

Basis and Derivation of Criterion

The animal carcinogenicity studies of Norris (1977), Quast, et al. (1977), and Maltoni, et al. (1977) and the epidemiological studies of O'Berg (1977) and Monson (1977) were considered to be the most pertinent data for the determination of a water quality criterion for the protection of human health. Although the epidemiological studies showed excesses of various cancers in man, neither study had quantitative exposure data of the workers to acrylonitrile and hence could not be utilized for calculation of a safe level.

The criterion was therefore developed from the animal carcinogenicity data by utilizing the linear non-threshold model (see Appendix A). The rat carcinogenicity studies, in general, showed a tumorigenic response to acrylonitrile whether exposure was by ingestion or inhalation. These data support the findings of the epidemiological studies.

To select data for the evaluation of an acceptable risk concentration, studies having the following attributes were chosen:

1. There was an increase in frequency of tumors in treated rats over control rats.
2. There was a low frequency of tumors in control rats.
3. Several dosage levels were tested so dose-response relationships could be interpreted.

To use the linear dose-response non-threshold model in calculating a water concentration that results in a risk of a carcinogenicity incidence of 1/100,000, the following assumptions were made for all calculations:

1. A maximum bioaccumulation factor of 110 for acrylonitrile, as determined for the bluegill sunfish (EPA report, Duluth, Mn.).
2. Consumption of water per person per day is 2 l over a period of 70 years.
3. Average consumption of fish per person per day is 18.7 grams.
4. Average life span for test rats is 730 days.

Specialized assumptions for converting inhalation dose to an equivalent ingestion dose were made with the Maltoni, et al. (1977) study as follows (also see Appendix B for sample calculation):

1. **The average rat respiration rate is 0.61 l/min. kg (Guyton, 1947; Crosfill and Widdiconbe, 1961).**
2. **The average weight for male rats is 500 g and female rats 300 g.**
3. **The absorption efficiency is 90 percent (Young, et al. 1977).**
4. **Since the duration of the experiment was 1001 days, the average life span of the rat was assumed to be 1001 days due to constraints of the equations in the linear model.**
5. **The data of Young, et al. (1977) (see Pharmacokinetics) suggests that extrapolation from one dosage route to another may not be valid. Further verification of this data is needed, however, and the data of Maltoni's inhalation study was included for comparison with the water ingestion studies.**

The results of the application of the linear non-threshold model to the selected data are summarized below:

Reference	Route	Location of tumor	Sex	Dose (mg/kg)	Acceptable risk concentration in water (mg/l)
Norris, 1977	water ingestion	proliferative lesions in brain	female	12.45	1.2×10^{-4}
		mammary gland	female	4.7	1.6×10^{-4}
		ear canal masses	female	12.45	9.8×10^{-4}
			male	23.8	8.8×10^{-5}
Quast, et al. 1977	water ingestion	stomach	female	27.45	1.5×10^{-4}
			male	23.8	8.8×10^{-5}
		central nervous system	female	11.4	8.3×10^{-5}
			male	9.6	1.9×10^{-4}
		zymbal gland	female	11.4	1.9×10^{-4}
Maltoni, et al. 1977	inhalation	gliomas	male	4.1*	18.1×10^{-4}
		mammary gland	female	1.0*	0.6×10^{-4}
			male	4.1*	5.6×10^{-4}

*Calculated ingestion dose converted from inhalation (Appendix B)

In spite of the differences between the data sets, the application of linear non-threshold model results in relatively similar calculated acceptable risk concentrations for water in each case. Due to the numerous assumptions necessary for the Maltoni study as well as the potential inability to convert between dosage routes, the data from this study were not weighed as heavily as the others. Therefore, the value of 0.8×10^{-4} mg/l was selected as the recommended criterion for acrylonitrile in water. It must be emphasized that this level is based on data from a 12-month interim report and is, therefore, preliminary in nature.

Under the Consent Decree in NRDC vs. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." Acrylonitrile is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of acrylonitrile in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and States in the possible future development of water quality regulations, the concentrations of acrylonitrile corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6} or 10^{-7} as shown in the table below.

Exposure Assumptions	Risk Levels and Corresponding Criteria (1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams of fish and shellfish (2)		0.008×10^{-4} ng/l	0.08×10^{-4} ng/l	0.8×10^{-4} ng/l
Consumption of fish and shellfish only.		0.016×10^{-4} ng/l	0.16×10^{-4} ng/l	1.6×10^{-4} ng/l

(1) Calculated by applying a modified "one hit" extrapolation model described in the Methodology Document to the animal bioassay data presented in Appendix III. Since the extrapolation model is linear to low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Fifty one percent of the acrylonitrile exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 110-fold. The remaining 49 percent of the acrylonitrile exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of acrylonitrile (1) occurring from the consumption of both drinking water and aquatic life grown in water containing the corresponding acrylonitrile concentrations and, (2) occurring solely from the consumption of aquatic life grown in the waters containing the corresponding acrylonitrile concentrations. Because data indicating other sources of exposure and the contribution to total body burden are inadequate for quantitative use, the criterion reflects the increment to risks associated with ambient water exposure only.

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APPENDIX I

Carcinogenicity Risk Assessment by Extrapolation from Laboratory Animal Toxicity Tests

An assessment of health risks associated with exposures of a general environmental nature requires prediction of effects from low level exposures of lifetime duration. Carcinogenic risks effects from environmental exposures must normally be estimated from animal data obtained at much higher levels because of the difficulty in detecting a small increase in tumor induction resulting from long-term low level exposure. Because the carcinogenic process is generally believed to be irreversible, self-replicating, and often orginating from a single somatic cell mutation, assumptions of threshold levels of effect are believed to be invalid for many, if not all, cancer-causitive compounds. Although many models have been proposed for extrapolation from animal data to human risk assessment, the one utilized here was chosen to facilitate uniform treatment of the variety of chemical compounds that are discussed in the development of those water criterion documents which deal with animal carcinogens.

It is recognized that the process of evaluating existing studies and resultant data in preparation for application of mathematical methods involves a high level of professional judgment. Many questions will necessarily arise due to the unique characteristics of the specific compounds under discussion and the tremendous variability in completeness and compatability among the available studies.

A general explanation of the evaluation and extrapolation procedures to be used are as follows:

1. Since the compounds discussed are known, or suspect, carcinogens, emphasis was placed on those studies with carcinogenic or mutagenic endpoints. In particular, those studies dealing with mammaliam species.
2. The extrapolation method employed is a mathematical procedure which uses a single dose and observed response of a toxicologic experiment to estimate a dose level for humans that will not increase the risk of tumors by more than a specified level (1 in 100,000) (Personal communication, Dr. Todd Thorsland, CAG, U.S. EPA, Washington, D.C.). Clearly this method is predicated on sound toxicologic test procedures. Hence, each included study was evaluated for adherence to sound toxicological and statistical principles.
3. Judgment was exercised in prioritizing the significance of toxicologic studies that use different routes of administration. In general, the preferred route of exposure is oral (food, water, or gavage) followed by intraperitoneal, intravenous, inhalation, or dermal routes of administration for the same species. However, in some instances, considerations of absorption rates required that other routes be evaluated.

The NCI's Ad Hoc Committee on the Evaluation of Low Levels of Environmental Chemical Carcinogens outlined two conditions that would render the extrapolation of animal carcinogenesis to man inappropriate. This committee reported to the Surgeon General as follows:

> "Any substance which is shown conclusively to cause tumors in animals should be considered carcinogenic and therefore a potential hazard for man. Exceptions should be considered only where the carcinogenic effect is clearly shown the results from physical rather than chemical induction or where the route of administration is shown to be grossly inappropriate in terms of conceivable human exposure."

4. After selection of the sound toxicologic studies that form the basis for development if a recommended criteria, a single dose and observed response was selected for the most "sensitive" sex (if both males and females were tested) according to the following method: Select the lowest dose which yields a tumor response rate that is greater than the control rate. If the standard controls and media control response rates are not significantly different ($a<0.05$), a combined rate was calculated from controls.

5. The extrapolation methods were applied independently to each selected dose and response pair. The lowest projected dose was selected as the "safe level" based on the available toxicologic studies, if judgment indicated equal confidence in the various dose-response pairs.
6. The calculated safe dose was evaluated along with the results from human studies to develop a recommended criteria.

Calculation of Estimated Safe Levels for Humans:

The specific data analyses performed along with required input data are described following in Mathematical Description of Extrapolation Method. This model provides the additional risk associated with ingestion of 2 liters of water per day and contaminated aquatic foods. Any other risks associated with air, food, or other exposure are not addressed by this model. A copy of the working data sheet is also included.

Mathematical Description of Extrapolation Method

A. Necessary information:

Nt = No. of animals (males or females) exposed to selected dose that developed tumors (all sites combined unless tumors appear to be related to route of administration, e.g., peritoneal tumors would not be included if intraperitoneal injection method is used).

Nt = Total number of animals (males or females) exposed to selected dose level.

nc = Number of control animals (males or females) with tumors.

NC = Total number of control animals (males or females).

Le = Actual maximum lifespan for test animals.

le = Length of exposure (no. of hours, days, weeks, etc.).

d = Average dose per unit of time (mg/kg).

w = Average weight of test animals (kg).

B. Necessary information from general literature:

70 kg = Average weight of man.

L = Theoretical average length of life for test species, unless specified in article. (See attached table for appropriate values).

F = Average weight of fish consumed per day, assumed 18.7 grams.

C. Necessary ecological information:

R = Bioaccumulation factor for edible portions of fish (Supplied by Environmental Research Laboratory, Duluth).

(Note: If a bioaccumulation factor is provided for the total fish or for some part other than the total edible portion (such as the fat) an attempt should be made to estimate factor for edible portion.)

D. Mathematical Model:

$$Pt = Pc + (1-Pc) \left[1 - e^{-t^3 BD} \right]$$

Where:

$Pt = nt \div Nt$ = Proportion of test animals with tumors.

$Pc = nc \div NC$ = Proportion of control animals with tumors.

$D = \frac{d \times le}{Le}$ = Lifespan weighted average dose level (mg/kg)/(unit of Time).

$B = \left\{ \ln \left[\frac{1 - Pt}{1 - Pc} \right] \right\} \div \left[D \times t^3 \right]$ where $t = \frac{\text{lifespan for test animals}}{\text{length of life for species}} = \frac{Le}{L}$

$B = B \sqrt[3]{\frac{70}{w}}$ (Note: It is assumed that average weight of man = 70 kg.)

If and only if $B < 0.1$ then

$SL = \frac{10^{-5} \times 70}{-B' (2+R \times F)}$ = Safe level (mg/l) for man

If $B \geq 0.1$ then

$SL = \frac{\ln (1 - 10^{-5})}{-B' (2+R \times F)} \times 70$ = Safe level (mg/l) for man

(Note: It is assumed average daily consumption of water is 2 liters/day.

Appendix II

Conversion of Inhalation Dosage to Ingestion Dosage for the Study of Maltoni, et al. (1977).

The following procedure was utilized to convert the inhalation dosage of Maltoni, et al. (1977) to equivalent ingestion dosage. The example uses a dose of 10 ppm; similar to calculations were made for the specific doses utilized by Maltoni.

1. Conversion of ppm to mg/m^3 was done by using the molecular weight of acrylonitrile and determining a conversion factor such that

   $mg/m^3 = ppm \times 2.18$

   Therefore $10 \text{ ppm} = 21.8 \text{ mg/m}^3$

2. The inhalation rate of the rat was assumed to be 0.61 1/min. kg. Correcting for the number of exposure hours per day the volume of respired air was determined.

$$\frac{\text{total air}}{\text{day}} = \frac{0.61 \text{ l}}{\text{min.kg}} \times \frac{60 \text{ min}}{\text{hr}} \times \frac{4 \text{ hour}}{\text{day}} \times \frac{m^3}{1000 \text{ l}} = \frac{0.1464 m^3}{\text{kg.day}}$$

3. Combining the results of 1. and 2. the air dose was determined.

$$mg/kg.d = 21.8 mg/m^3 \times \frac{0.1464 m^3}{\text{kg.day}} = \frac{3.1915 \text{ mg}}{\text{kg.day}}$$

4. A figure of 90 percent absorption was taken from Young, et al. (1977). This study was more detailed and felt to be more precise than that of Rogaczewska and Piotrowsky (1968) which indicated 46 percent. The absorption figure was used to convert inhaled dose to the retained dose which was assumed to be equivalent to ingested dose.

$$\frac{3.1915 \text{ mg}}{\text{kg.day}} \times 0.90 = \frac{2.872 \text{ mg}}{\text{kg.day}} \text{ ingested dose}$$

5. Because dosing was for only 5 days/week the value in 4. was corrected to a 7 days/week exposure.

$$\text{equivalent weekly dose} = \frac{2.872\text{mg}}{\text{kg.d}} \times \frac{5}{7} = \frac{2.051\text{mg}}{\text{kg.d}}$$

6. Therefore, an inhalation dosage of 10 ppm is estimated to be equivalent to an ingested dosage of

$$\frac{2.051\ \text{mg}}{\text{kg.day}}$$

APPENDIX III

Summary and Conclusions Regarding the Carcinogenicity of Acrylonitrile (AN) *

Acrylonitrile has a molecular structure (CH_2=CH-CN), which resembles that of vinyl chloride (CH_2=CH-Cl), a chemical known to cause animal and human cancer. Principally, it is used as an intermediate in the manufacture of a wide variety of acrylic fibers, plastics, and in synthetic rubber.

Acrylonitrile is mutagenic in the Ames _Salmonella typhimurium_ strains TA1535, TA1538, and TA1978 in the presence of mammalian metabolic activation which indicates both base-pair substitution and frameshift mechanisms of action. It is also reported positive in _Drosophila_.

There is strong preliminary evidence that acrylonitrile is likely to be a human carcinogen. This conclusion is based on the following studies. 1) two preliminary reports of the Dow Chemical Co. bioassay of acrylonitrile given in drinking water to Sprague-Dawley rats, 2) carcinogenicity of acrylonitrile in Sprague-Dawley rats by Maltoni, administered via inhalation. In these three studies, acrylonitrile has induced excess tumor incidence of the central nervous system as compared to the controls, 3) in addition, a preliminary epidemiologic study by E.I. Dupont de Nemours and Co., Inc. indicated an excess of lung and colon cancer incidence among active employees in the company working with acrylonitrile as compared to that of the national experience.

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*This summary has been prepared and approved by the Carcinogens Assessment Group of U.S. EPA on June 15, 1979.

In summary, carcinogenic responses have been induced in Sprague-Dawley rats and humans. These results, together with the positive mutagenic response, constitute clear evidence that acrylonitrile is likely to be a human carcinogen.

The water quality criterion for acrylonitrile is based on tumor incidence of the central nervous system at the 100 ppm dose level in female Sprague-Dawley rats observed and reported by the Dow Chemical Co. (interim report by Quast, et al. 1977). It is concluded that the water concentration of acryloitrile should be less than 0.084 µg/l in order to keep the lifetime cancer risk below 10^{-5}.

Summary of Pertinent Data

The water quality criterion for acrylonitrile is derived from the tumorigenic effect observed in the central nervous system of female Sprague-Dawley rats given 100 ppm acrylonitrile in drinking water. The time weighted average dose of 11.4 mg/kg/day was given for 52 weeks, and ten animals of each group were then sacrificed (interim). The incidence of brain tumors was 0/9 and 4/10 in the control and the treated groups, respectively. Assuming a fish bioconcentration of 110, the criterion is calculated from the following parameters:

$n_t = 4$ $d = 11.4$ mg/kg/day
$N_t = 10$ $R = 110$
$n_c = 0$ $L = 730$ days
$N_c = 9$ $w = 0.350$ kg
$le = 368$ days $F = 0.0187$ kg/day
$Le = 368$ days

Based on these parameters, the one-hit slope B_H is 2.0455 $(\text{mg/kg/day})^{-1}$. The resulting water concentration of acrylonitrile calculated to keep the individual risk below 10^{-5} is 0.084 µg/l. It must be emphasized that this concentration level is based on data from a 12-month interim report and is, therefore, likely to be modified when the final report becomes available.